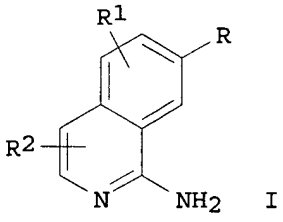
AN 1999:184268 CAPLUS
DN 130:223587
TI 1-amino-7-isoquinoline derivatives as serine protease inhibitors
IN Liebeschuetz, John Walter; Wylie, William Alexander; Waszkowycz, Bohdan; Murray, Christopher William; Rimmer, Andrew David; Welsh, Pauline Mary; Jones, Stuart Donald; Roscoe, Jonathan Michael Ernest; Young, Stephen Clinton; Morgan, Phillip John; Camp, Nicholas Paul; Crew, Andrew Philip Austin
PA Proteus Molecular Design Ltd., UK
SO PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9911657	A1	19990311	WO 1998-GB2600	19980828 <--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9888753	A1	19990322	AU 1998-88753	19980828
	EP 1012166	A1	20000628	EP 1998-940425	19980828
	R: CH, DE, ES, FR, GB, IT, LI, NL				
	US 6262069	B1	20010717	US 2000-485677	20000225
	US 2002040144	A1	20020404	US 2001-865418	20010529
	US 6420438	B1	20020716	US 2000-865418	20010529
PRAI	GB 1997-18392	A	19970829		
	GB 1998-3173	A	19980213		
	WO 1998-GB2600	W	19980828		
	US 2000-485677	A1	20000225		

OS MARPAT 130:223587
GI



I

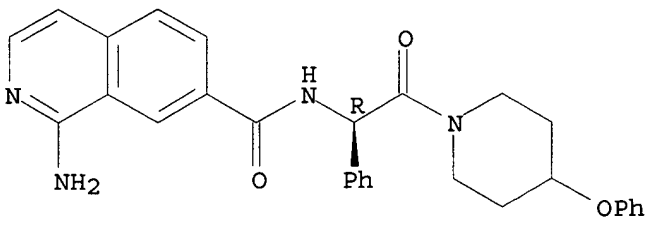
AB Aminoisoquinoline amino acid derivs. I [R1 = H, halo, cyano, nitro, hydroxy, amino, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, thiol, alkylthio, aminosulfonyl, alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or alkylamino (optionally substituted); R2 = H, halo, Me, amino, hydroxy, or oxo; and R is X-X-Y(R7)-L-Lp(D)n, where each X independently is a C, N, O or S atom or a CO, CR1, CR12 or NR1 group; Y is a nitrogen atom or a CR1 group or Y and L taken together form a cyclic group; R7 is a lipophilic group selected from alkyl, alkenyl, mono- or bi-cycloalkyl, aryl, heteroaryl, mono- or bicycloalkylalkyl, mono- or bicycloalkylalkenyl, aralkyl, heteroaryl-alkyl, arylalkenyl, heteroarylalkenyl, all optionally substituted by a group R1; L is an org. linker group contg. 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic

group; Lp is a lipophilic org. group selected from alkyl, heterocyclic, alkenyl, alkaryl, cycloalkyl, polycycloalkyl, cycloalkenyl, aryl, aralkyl or haloalkyl group or a combination of two or more such groups optionally substituted by one or more of oxa, thia, aza or R1 groups; D is a hydrogen bond donor group; and n is 0, 1, or 2] or their 3,4-dihydro derivs. were prepd. as serine protease inhibitors. Thus, 1-aminoisoquinolin-7-oyl-D-phenylglycine-4-methoxybenzylamide was prepd. by amidation of Boc-D-phenylglycine with 4-methylbenzylamine, followed by deprotection and coupling with 1-aminoisoquinoline-7-carboxylic acid trifluoroacetate.

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IN 7-Isoquinolinecarboxamide, 1-amino-N-[(1R)-2-oxo-2-(4-phenoxy-1-piperidinyl)-1-phenylethyl]- (9CI)
MF C29 H28 N4 O3

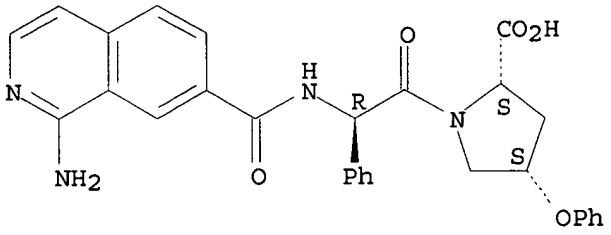
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

IN L-Proline, (2R)-N-[(1-amino-7-isoquinolinyl)carbonyl]-2-phenylglycyl-4-phenoxy-, (4S)- (9CI)
MF C29 H26 N4 O5

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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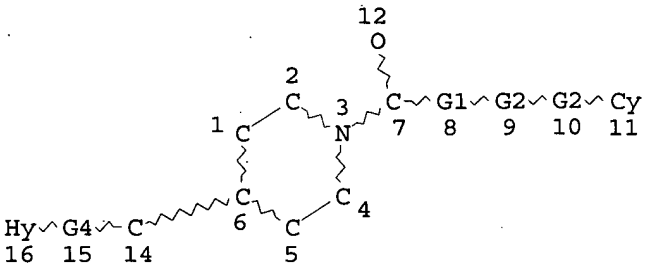
L6 STR



VAR G1=C/N
VAR G2=O/C/S/N
VAR G4=O/N
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 11
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE

=> s l6 ful
FULL SEARCH INITIATED 14:52:33 FILE 'REGISTRY'
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100.0% PROCESSED 49599 ITERATIONS 6 ANSWERS
SEARCH TIME: 00.00.02

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=> s l8
L9            5 L8

=> d bib abs hitstr 1-5

L9   ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2003 ACS
AN   2002:964146  CAPLUS
DN   138:39187
TI   Preparation of piperidinecarboxylates and related compounds as NMDA NR2B
     receptor antagonists for the treatment or prevention of migraine.
IN   Allen, Christopher; Koblan, Ken S.; Sleeth, Timothy
PA   Merck & Co., Inc., USA
SO   PCT Int. Appl., 185 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
PI   WO 2002100352      A2    20021219      WO 2002-US21069  20020607
     WO 2002100352      A3    20030327
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
             UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI US 2001-297672P   P    20010612
AB   A method for treating or preventing migraines comprises administration of
     an NR2B receptor antagonist (no data). The invention also encompasses the
     combination of an NR2B antagonist with a cyclooxygenase-2 selective
     inhibitor, a calcitonin gene-related peptide receptor (CGRP) ligand, a
     leukotriene receptor antagonist, or a 5HT1B/1D agonist for the treatment
     or prevention of migraines. Thus, 4-hydroxybenzoic acid,
     1-hydroxybenzotriazole hydrate, benzyl 4-(aminomethyl)piperidine-1-
     carboxylate (prepn. given), and Et3N in DMF were treated with
     1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and the mixt.
     allowed to stir at room temp. for 18 h to give 4-[(4-
     hydroxybenzoylamino)methyl]piperidine-1-carboxylic acid benzyl ester.
IT   455266-25-8P
     RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
     (Uses)
        (prepn. of piperidinecarboxylates and related compds. as NR2B receptor
        antagonists for the treatment or prevention of migraine)
RN   455266-25-8  CAPLUS
CN   4-Piperidinemethanamine, 1-[1-oxo-4-(2-thienyl)butyl]-N-2-pyrimidinyl-
     (9CI)  (CA INDEX NAME)
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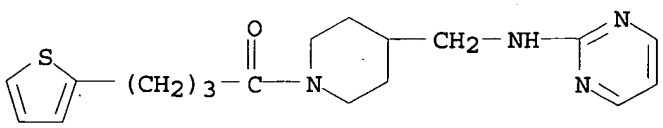


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L9   ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2003 ACS
AN   2002:676010  CAPLUS
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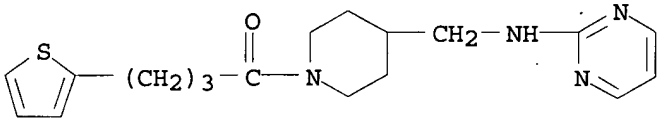
DN 137:216875
TI Preparation of N-acyl-4-(heterocyclylaminomethyl)piperidines as NMDA/NR2B antagonists
IN Claiborne, Christopher F.; Butcher, John W.; Claremon, David A.; Libby, Brian E.; Liverton, Nigel J.; Munson, Peter M.; Nguyen, Kevin T.; Phillips, Brian; Thompson, Wayne; McCauley, John A.
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 208 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002068409	A1	20020906	WO 2002-US5226	20020220

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002165241	A1	20021107	US 2002-79452	20020220
PRAI US 2001-271100P	P	20010223		

OS MARPAT 137:216875
AB BQ1(X)ANHQ2 [Q1 = 5-7 membered N-contg. nonarom. ring, azabicyclooctyl; Q2 = 5-6 membered (substituted) heteroaryl ring; A = alkylene; B = Ar(CH2)0-3O2C, Ar(CH2)0-3SO2, etc.; Ar = (substituted) aryl, heteroaryl; X = H, OH, F, alkyl, alkoxy, NH2, O], were prepd. Thus, 1-[(benzyloxy)carbonyl]-4-piperidinecarboxylic acid, 4-aminopyridine, EDC, and HOAt were kept 4 h in DMF to give the amide, which was reduced with BH3.THF to give benzyl 4-[(4-pyridylamino)methyl]-1-piperidinecarboxylate. Title compds. showed IC50's of <50 .mu.M for inhibition of NR1A/2B NMDA receptor activation.
IT **455266-25-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compd.; prepn. of N-acyl-4-(heterocyclylaminomethyl)piperidines as NMDA/NR2B antagonists)
RN 455266-25-8 CAPLUS
CN 4-Piperidinemethanamine, 1-[1-oxo-4-(2-thienyl)butyl]-N-2-pyrimidinyl- (9CI) (CA INDEX NAME)



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

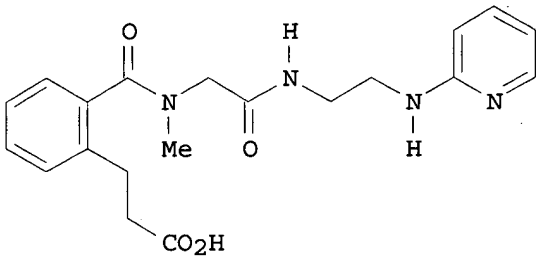
L9 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2002:484686 CAPLUS
DN 137:47124
TI Preparation of 2-[(carbamoylmethyl)carbamoyl]phenylpropanoates and analogs as .alpha.v.beta.3 integrin receptor ligands
IN Geneste, Herve; Kling, Andreas; Lange, Udo; Lauterbach, Arnulf; Seitz, Werner; Graef, Claudia Isabella; Subkowski, Thomas; Hornberger, Wilfried;

Kluge, Michael; Spriesterbach, Rainer
PA Knoll A.-G., Germany
SO Ger. Offen., 62 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10064823	A1	20020627	DE 2000-10064823	20001222
WO 2002051810	A2	20020704	WO 2001-EP14924	20011218
WO 2002051810	A3	20030320		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI DE 2000-10064823 A 20001222
OS MARPAT 137:47124
GI

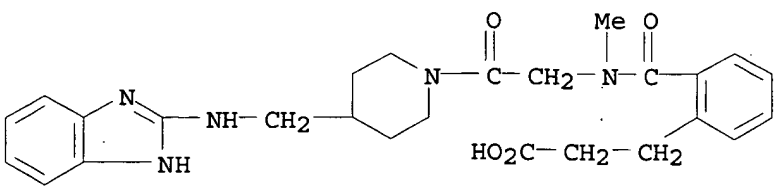


I

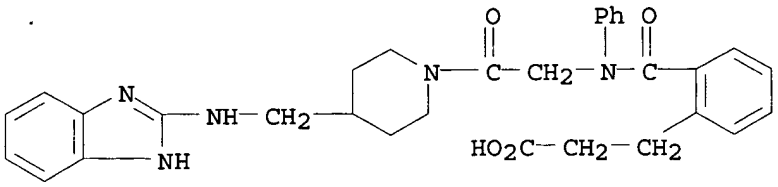
AB Title compds. were prepd. as .alpha.v.beta.3 integrin receptor ligands (no data). Thus, 2-(OHC)C6H4CO2H was condensed with (EtO)2P(O)CH2CO2Me and the hydrogenated product amidated by MeNHCH2CO2CMe3 to give, after sapon., 2-(HO2CH2CH2C)C6H4CONMeCH2CO2H which was amidated by N-(2-pyridinyl)ethandiamine to give, after sapon., title compd. I.

IT **438633-38-6P 438633-41-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-[(carbamoylmethyl)carbamoyl]phenylpropanoates and analogs as .alpha.v.beta.3 integrin receptor ligands)

RN 438633-38-6 CAPLUS
CN Benzenepropanoic acid, 2-[[[2-[4-[(1H-benzimidazol-2-ylamino)methyl]-1-piperidinyl]-2-oxoethyl]methylamino]carbonyl]- (9CI) (CA INDEX NAME)



RN 438633-41-1 CAPLUS
CN Benzenepropanoic acid, 2-[[[2-[4-[(1H-benzimidazol-2-ylamino)methyl]-1-piperidinyl]-2-oxoethyl]phenylamino]carbonyl]- (9CI) (CA INDEX NAME)



L9 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2001:923766 CAPLUS
DN 136:54019
TI Preparation of amino acid derivatives as serine protease inhibitors
IN Liebeschuetz, John Walter; Murray, Christopher William; Young, Stephen Clinton; Camp, Nicholas Paul; Jones, Stuart Donald; Wylie, William Alexander; Masters, John Joseph; Wiley, Michael Robert; Sheehan, Scott Martin; Engel, David Birenbaum; Watson, Brian Morgan
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001096304	A1	20011220	WO 2001-GB2572	20010612
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	WO 2000076971	A2	20001221	WO 2000-GB2302	20000613
	WO 2000076971	A3	20010802		
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	EP 1289953	A1	20030312	EP 2001-938403	20010612
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2002151724	A1	20021017	US 2002-30186	20020204
PRAI	WO 2000-GB2302	W	20000613		
	GB 2000-30306	A	20001213		
	GB 1999-13823	A	19990614		
	US 1999-142064P	P	19990702		
	GB 1999-18741	A	19990809		
	GB 1999-29553	A	19991214		
	WO 2001-GB2572	W	20010612		

OS MARPAT 136:54019

AB Compds. R2-X-X-Y(Cy)-L-Lp(D)n [R2 is a 5- or 6-membered arom. carbon ring optionally interrupted by a N, O or S ring atom, optionally substituted at the 3 and/or 4 position or forms a fused ring system at these positions, which is an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring, or substituted at the position alpha to X-X; X is a C, N, O or S atom or a CO, CR1a, C(R1a)2 or NR1a group, where R1a represents H, OH, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by OH, alkylamino, alkoxy, oxo, aryl or cycloalkyl; Y is a N atom or a CR1b group (R1b defined as for R1a); Cy is an (un)substituted, (un)satd., mono- or polycyclic, homo- or heterocyclic group; -L-Lp(D)n is 3-(Rq-CH2)-1-pyrrolidinylcarbonyl or 4-(Rq-CH2)-1-piperidinylcarbonyl, where Rq is an amino group] or their physiol.-tolerable salts were prepd. for use as serine protease and factor Xa inhibitors in the treatment of cardiovascular disorders. Compds. of the invention were found to significantly elongate the partial thromboplastin time (prothrombin time). Thus, 1-[(4-methoxybenzoyl-D-phenylglycinyl)]-4-[(isopropylamino)methyl]piperidine hydrochloride was prepd. in the first of 28 examples.

IT **381216-02-0P**

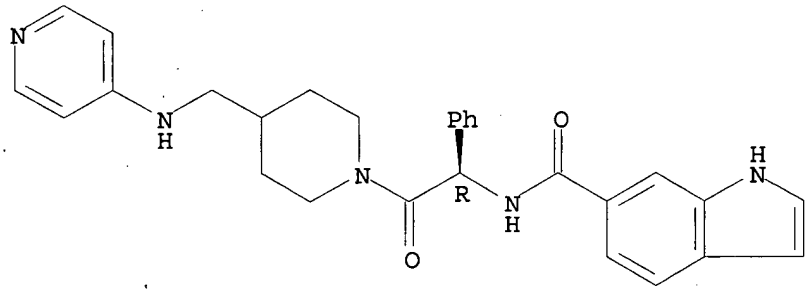
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of amino acid derivs. as serine protease inhibitors)

RN 381216-02-0 CAPLUS

CN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-[(4-pyridinylamino)methyl]-1-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS

AN 2001:661421 CAPLUS

DN 135:226988

TI Preparation of condensed thiazolamines as neuropeptide Y5 antagonists

IN Schmidlin, Tibur; Rueeger, Heinrich; Gerspacher, Marc

PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft M.B.H.

SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001064675	A1	20010907	WO 2001-EP2339	20010301

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OS MARPAT 135:226988

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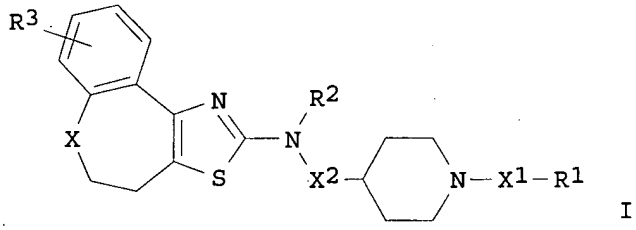

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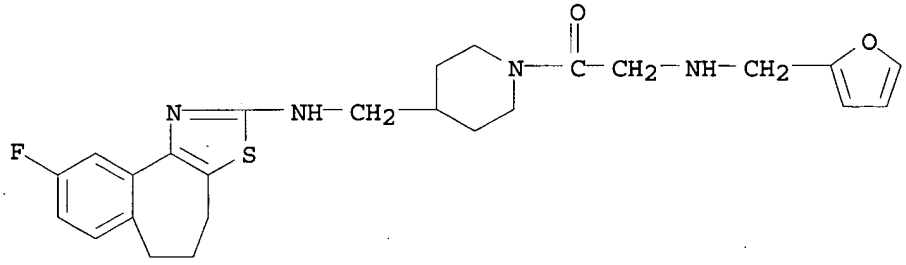
AB The title compds. [I; R1 = (un)substituted alkyl, cycloalkyl, Ph, etc.; R2 = H, SO3H, PO3H2; R3 = H, alkyl, alkoxy, etc.; X = CH2, O; X1 = CO, SO2; X2 = alkylene] and their pharmaceutically acceptable salts which act against the binding of the neuropeptide Y (NPY) to the Y5-receptor subtype (NPY-antagonism), and might be used in particular for the treatment of adiposity, were prepd. and formulated. E.g., a multi-step synthesis of I [R1 = Me; R2 = H; R3 = 9-F; X = CH2; X1 = CO; X2 = CH2] which showed a redn. in food intake of 57% in rats, was given.

IT **359017-45-1P 359018-33-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of condensed thiazolamines as neuropeptide Y5 antagonists)

RN 359017-45-1 CAPLUS

CN 4-Piperidinemethanamine, N-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[1,2-d]thiazol-2-yl)-1-[[(2-furanylmethyl)amino]acetyl]- (9CI) (CA INDEX NAME)



RN 359018-33-0 CAPLUS

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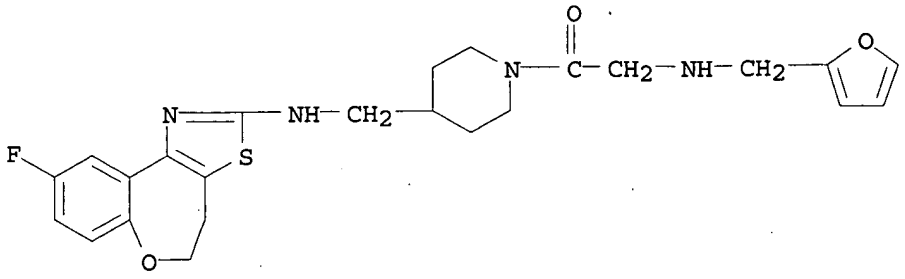

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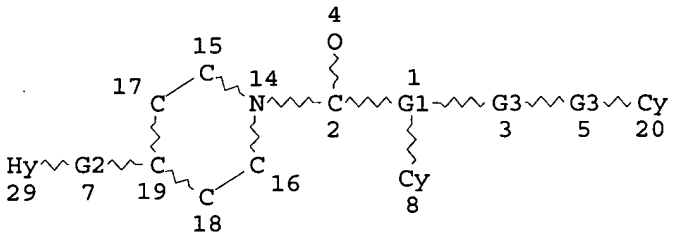

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STEREO ATTRIBUTES: NONE

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L9 41 ANSWERS REGISTRY COPYRIGHT 2003 ACS
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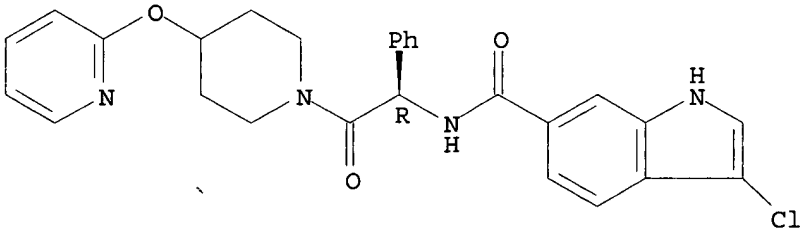
CI COM

Absolute stereochemistry.



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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 20 Jun 2003  VOL 138 ISS 26
FILE LAST UPDATED: 19 Jun 2003  (20030619/ED)

  This file contains CAS Registry Numbers for easy and accurate
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L10           3 L9

=> d bib 1-3

L10  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2003 ACS
AN   2001:923758  CAPLUS
DN   136:37946
TI   Preparation of amino acid derivatives as serine protease inhibitors
IN   Liebeschuetz, John Walter; Murray, Christopher William; Young, Stephen
     Clinton; Camp, Nicholas Paul; Jones, Stuart Donald; Wylie, William
     Alexander; Masters, John Joseph; Wiley, Michael Robert; Sheehan, Scott
     Martin; Engel, David Birenbaum; Watson, Brian Morgan
PA   Eli Lilly and Company, USA
SO   PCT Int. Appl., 142 pp.
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OS   MARPAT 136:37946
RE.CNT  3      THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L10  ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2003 ACS
AN   2000:900614  CAPLUS
DN   134:56958
TI   Preparation of amino acid derivatives as serine protease inhibitors
IN   Liebeschuetz, John Walter; Lyons, Amanda Jane; Murray, Christopher
     William; Rimmer, Andrew David; Young, Stephen Clinton; Camp, Nicholas
     Paul; Jones, Stuart Donald; Morgan, Phillip John; Richards, Simon James;
     Wylie, William Alexander; Masters, John Joseph; Wiley, Michael Robert
PA   Eli Lilly and Company, USA; Protherics Molecular Design Limited
SO   PCT Int. Appl., 261 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 13
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OS  MARPAT 134:56958
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L10 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 2000:900613 CAPLUS
DN 134:56957
TI Preparation of amino acid derivatives as serine protease inhibitors
IN Liebeschuetz, John Walter; Lyons, Amanda Jane; Murray, Christopher William; Rimmer, Andrew David; Young, Stephen Clinton; Camp, Nicholas Paul; Jones, Stuart Donald; Morgan, Phillip John; Richards, Simon James; Wylie, William Alexander; Lively, Sarah Elizabeth; Harrison, Martin James; Waszkowycz, Bohdan; Masters, John Joseph; Wiley, Michael John
PA Eli Lilly and Company, USA; Protherics Molecular Design Limited
SO PCT Int. Appl., 350 pp.
CODEN: PIXXD2
DT Patent
LA English
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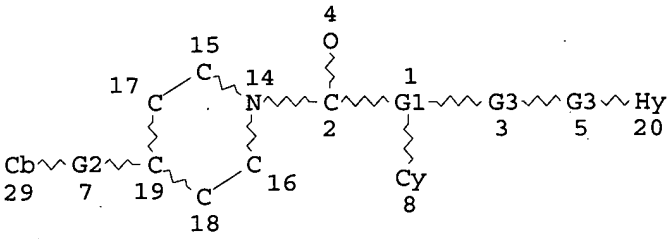


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MF   C29 H28 N4 O3
SR   CA
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Absolute stereochemistry.
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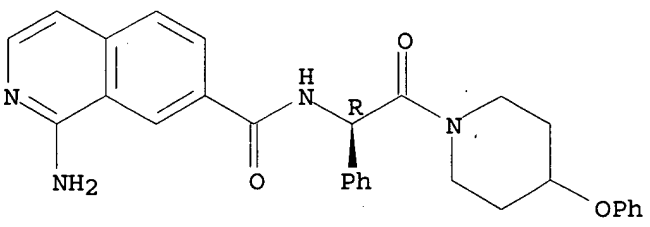

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1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

AN 1995:807929 CAPLUS
DN 123:227995
TI Preparation of guanidinyl- or amidinyl-substituted N-acylpyrrolidines and N-acylpiperidines as thrombin inhibitors.
IN Kimball, Spencer D.; Das, Jagabandhu; Lau, Wan Fang
PA Bristol-Myers Squibb Co., USA
SO Eur. Pat. Appl., 81 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 6

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JP 06340619	A2	19941213	JP 1994-88296	19940426
CA 2122646	AA	19941104	CA 1994-2122646	19940502
AU 9461837	A1	19941110	AU 1994-61837	19940502
AU 669432	B2	19960606		
PRAI US 1993-56017	A	19930503		

OS MARPAT 123:227995
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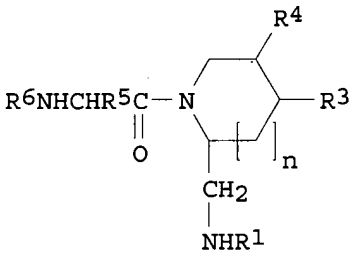

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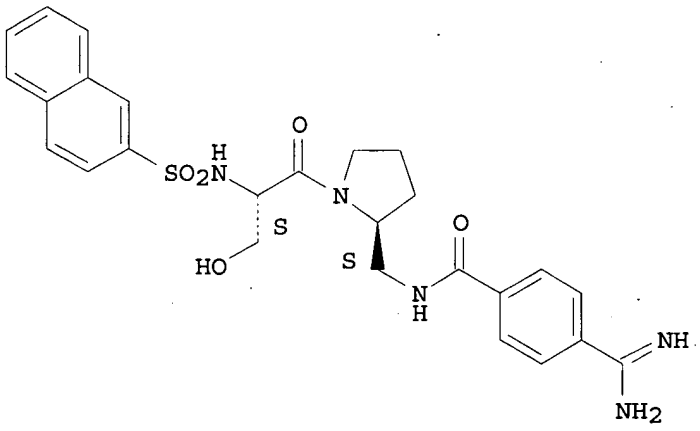


II

AB Guanidinyl- or amidinyl-substituted N-acylpyrrolidines and N-acylpiperidines I (n = integer; R1 = guanidine, amidine, amino-linking group; R3, R4 = H, alkyl, cycloalkyl, etc.; R5 = H, hydroxyalkyl, etc.; R6 = H, carboxy, etc.) were disclosed as thrombin inhibitors. A specifically claimed example compd. is amidino-N-[[[hydroxy[[(naphthalenyl)sulfonyl]amino]oxopropyl]pyrrolidinyl]methyl]benzamide II.

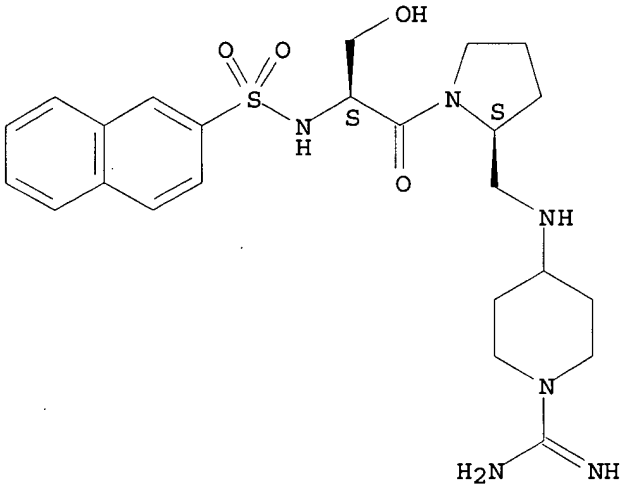
IT **168050-92-8**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of guanidinyl- or amidinyl- pyrrolidines or piperidines antithrombotics)

RN 168050-92-8 CAPLUS

CN 2-Pyrrolidinemethanamine, N-[1-(aminoiminomethyl)-4-piperidinyl]-1-[3-hydroxy-2-[(2-naphthalenylsulfonyl)amino]-1-oxopropyl]-, [S-(R*,R*)]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L1 HAS NO ANSWERS
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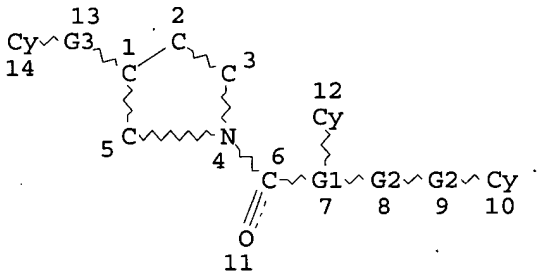

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 1
NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE

=> s l1 ful
FULL SEARCH INITIATED 14:03:14 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 19331 TO ITERATE

100.0% PROCESSED 19331 ITERATIONS 12 ANSWERS
SEARCH TIME: 00.00.02

L3 12 SEA SSS FUL L1

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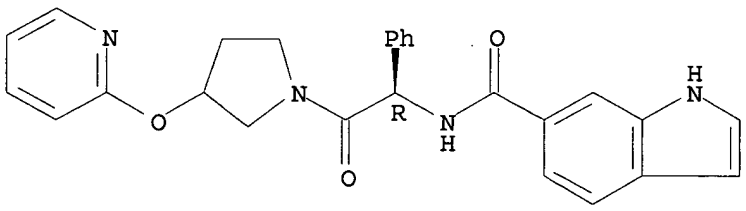
L3 ANSWER 1 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-49-2 REGISTRY
CN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(2-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H24 N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

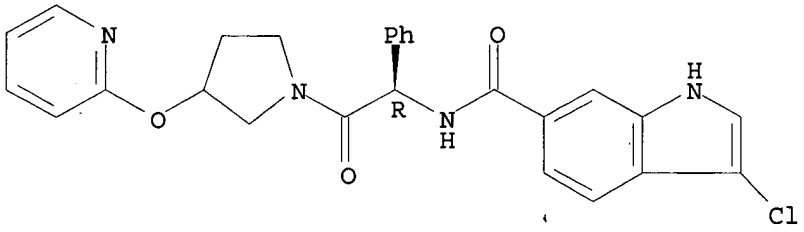


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 2 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-48-1 REGISTRY
CN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(2-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H23 Cl N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

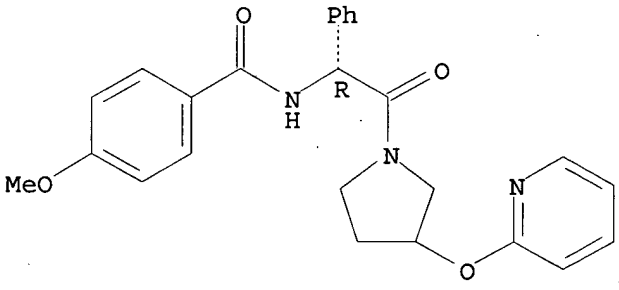


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 3 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-47-0 REGISTRY
CN Benzamide, 4-methoxy-N-[(1R)-2-oxo-1-phenyl-2-[3-(2-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H25 N3 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



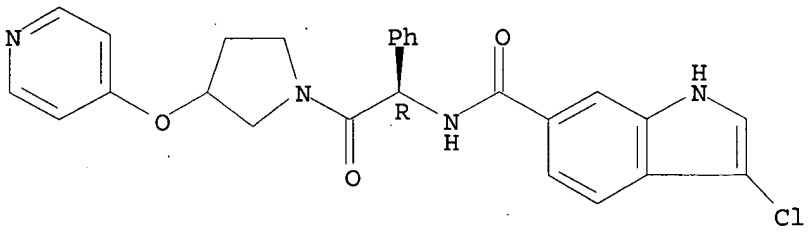
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 4 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-46-9 REGISTRY

CN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H23 Cl N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

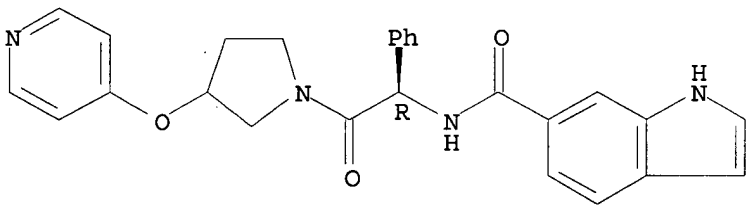


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 5 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-45-8 REGISTRY
CN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H24 N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

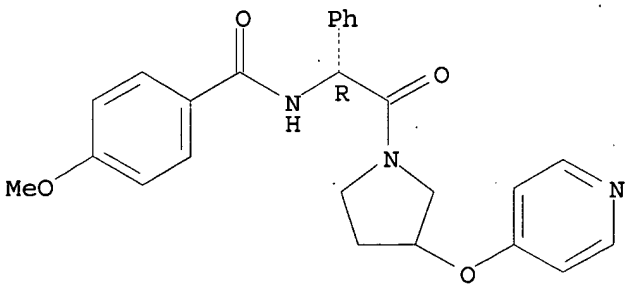


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 6 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-44-7 REGISTRY
CN Benzamide, 4-methoxy-N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H25 N3 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

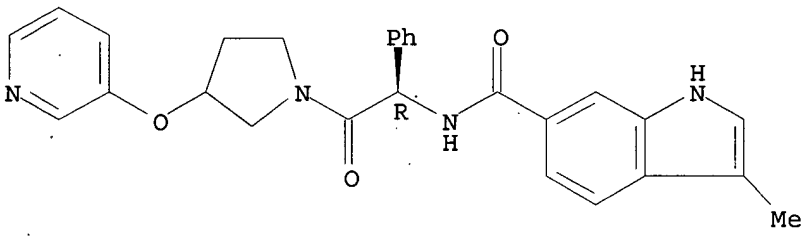


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 7 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-04-9 REGISTRY
CN 1H-Indole-6-carboxamide, 3-methyl-N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H26 N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

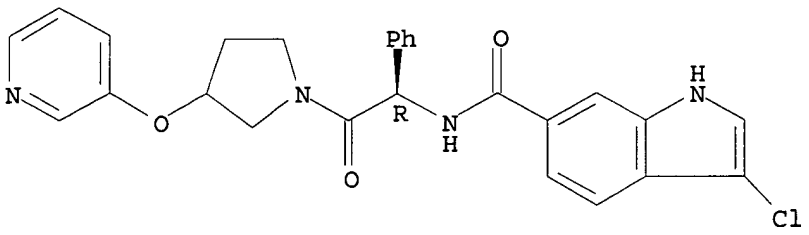


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 8 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-03-8 REGISTRY
CN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H23 Cl N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

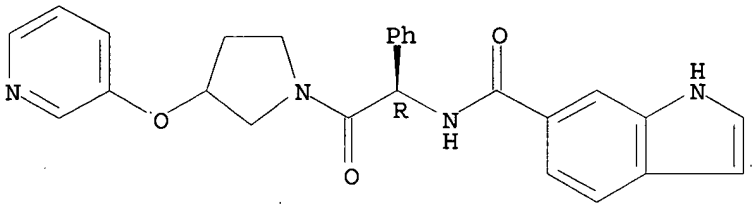


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 9 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-02-7 REGISTRY
CN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H24 N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

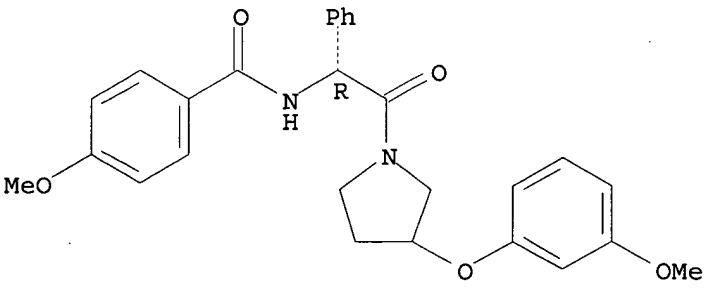


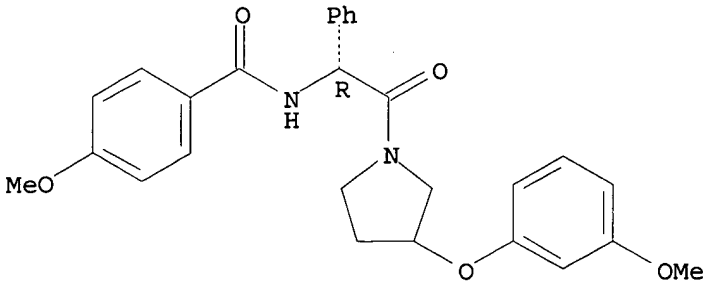
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313487-90-0 REGISTRY
CN Benzamide, 4-methoxy-N-[(1R)-2-[3-(3-methoxyphenoxy)-1-pyrrolidinyl]-2-oxo-1-phenylethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H28 N2 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



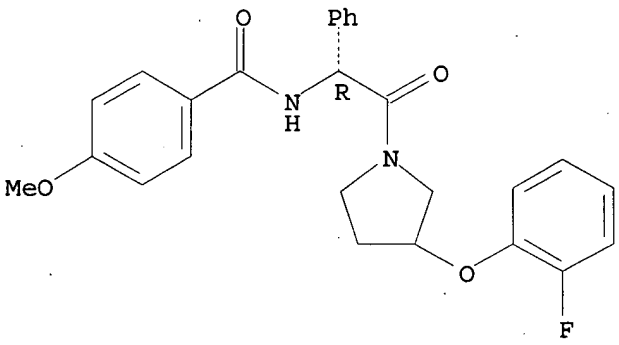


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313487-89-7 REGISTRY
CN Benzamide, N-[(1R)-2-[3-(2-fluorophenoxy)-1-pyrrolidinyl]-2-oxo-1-phenylethyl]-4-methoxy- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H25 F N2 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

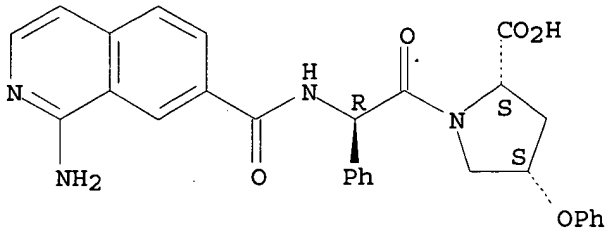


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 12 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 221050-61-9 REGISTRY
CN L-Proline, (2R)-N-[(1-amino-7-isoquinolinyl)carbonyl]-2-phenylglycyl-4-phenoxy-, (4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H26 N4 O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



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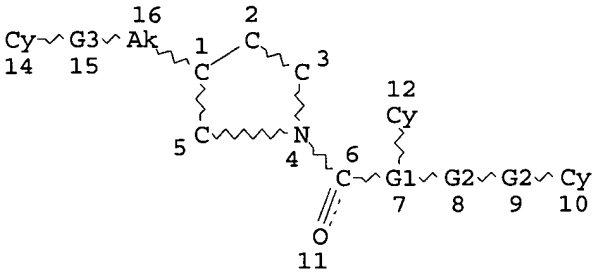
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

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  4.8% PROCESSED    1000 ITERATIONS                                  0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       403800 TO   420960
PROJECTED ANSWERS:               0 TO        0

L8            0 SEA SSS SAM L7

=> s l7 ful
FULL SEARCH INITIATED 14:07:53 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 413103 TO ITERATE

 96.0% PROCESSED  396435 ITERATIONS                                0 ANSWERS

 96.8% PROCESSED  400000 ITERATIONS                                0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.21

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       413103 TO   413103
PROJECTED ANSWERS:               0 TO        0

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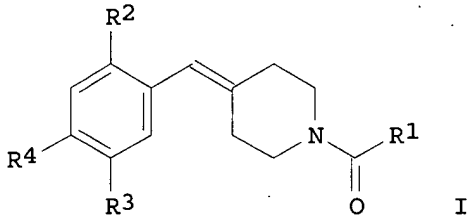
AN 2002:488375 CAPLUS
DN 137:216843
TI Synthesis and Evaluation of 2'-Substituted 4-(4'-Carboxy- or 4'-carboxymethylbenzylidene)-N-acylpiperidines: Highly Potent and in Vivo Active Steroid 5.alpha.-Reductase Type 2 Inhibitors
AU Picard, Franck; Barassin, Stephan; Mokhtarian, Armand; Hartmann, Rolf W.
CS Pharmaceutical and Medicinal Chemistry, Saarland University, Saarbruecken, D-66041, Germany
SO Journal of Medicinal Chemistry (2002), 45(16), 3406-3417
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 137:216843
GI



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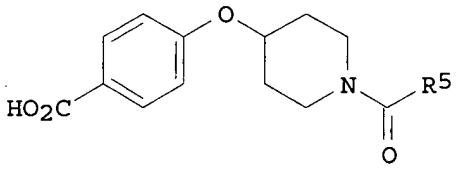
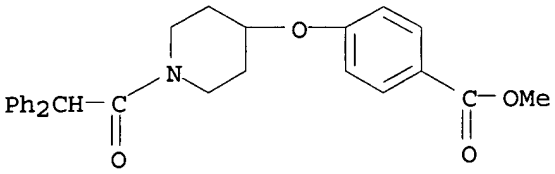


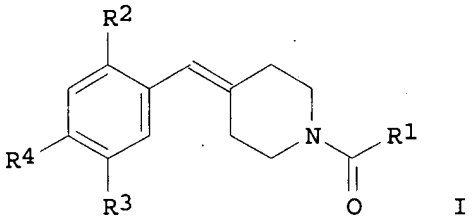
II

AB Sixteen N-acylpiperidines I (R1 = Ph2CH, Ph2CHCH2, dicyclohexylmethyl, 1-adamantyl; R2 = H, F, MeO; R3 = H, HO2C; R4 = H, HO2C, HO2CCH2) and II (R5 = Ph2CH, Ph2N, Me3CO, 1-adamantyl), bearing carboxylic acid moieties, were synthesized and evaluated for inhibition of rat and human steroid 5.alpha.-reductase isoenzymes types 1 and 2. In the dicyclohexylacetyl series (R1 = dicyclohexylmethyl), fluorination in the 2-position of the benzene nucleus, exchange of the carboxy group by a carboxymethyl moiety, and combination of both structural modifications led to highly active inhibitors of the human type 2 isoenzyme [IC50 values: I [R2 = F, R3 = H, R4 = HO2C; (III)], 11 nM; I (R2 = R3 = H, R4 = HO2CCH2), 6 nM; I (R2 = F, R3 = H, R4 = HO2CCH2), 7 nM; finasteride, 5 nM]. In vivo all compds. tested markedly reduced the prostate wts. in castrated testosterone-treated rats. Oral activity was shown for compd. I (R1 = dicyclohexylmethyl, R2 = R3 = H, R4 = HO2C). From the finding that III is active in the rat, although it is a rather poor inhibitor of the rat enzyme and is a strong inhibitor of the human enzyme, it is concluded that it should be highly potent in men.
IT **455323-67-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of steroid 5.alpha.-reductase inhibiting acylpiperidines via N-acylation of phenoxypiperidines)
RN 455323-67-8 CAPLUS
CN Benzoic acid, 4-[[1-(diphenylacetyl)-4-piperidinyl]oxy]-, methyl ester (9CI) (CA INDEX NAME)



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 2002:488375 CAPLUS
DN 137:216843
TI Synthesis and Evaluation of 2'-Substituted 4-(4'-Carboxy- or 4'-carboxymethylbenzylidene)-N-acylpiperidines: Highly Potent and in Vivo Active Steroid 5.alpha.-Reductase Type 2 Inhibitors
AU Picard, Franck; Barassin, Stephan; Mokhtarian, Armand; Hartmann, Rolf W.
CS Pharmaceutical and Medicinal Chemistry, Saarland University, Saarbruecken, D-66041, Germany
SO Journal of Medicinal Chemistry (2002), 45(16), 3406-3417
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 137:216843
GI



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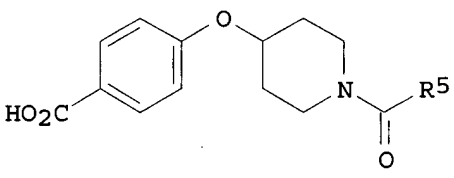
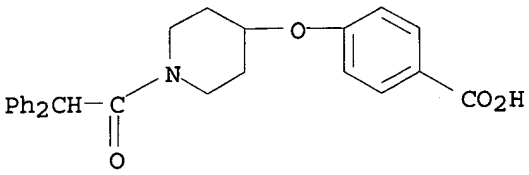


II

AB Sixteen N-acylpiperidines I (R1 = Ph2CH, Ph2CHCH2, dicyclohexylmethyl, 1-adamantyl; R2 = H, F, MeO; R3 = H, HO2C; R4 = H, HO2C, HO2CCH2) and II (R5 = Ph2CH, Ph2N, Me3CO, 1-adamantyl), bearing carboxylic acid moieties, were synthesized and evaluated for inhibition of rat and human steroid 5.alpha.-reductase isoenzymes types 1 and 2. In the dicyclohexylacetyl series (R1 = dicyclohexylmethyl), fluorination in the 2-position of the benzene nucleus, exchange of the carboxy group by a carboxymethyl moiety, and combination of both structural modifications led to highly active inhibitors of the human type 2 isoenzyme [IC50 values: I [R2 = F, R3 = H, R4 = HO2C; (III)], 11 nM; I (R2 = R3 = H, R4 = HO2CCH2), 6 nM; I (R2 = F, R3 = H, R4 = HO2CCH2), 7 nM; finasteride, 5 nM]. In vivo all compds. tested markedly reduced the prostate wts. in castrated testosterone-treated rats. Oral activity was shown for compd. I (R1 = dicyclohexylmethyl, R2 = R3 = H, R4 = HO2C). From the finding that III is active in the rat, although it is a rather poor inhibitor of the rat enzyme and is a strong inhibitor of the human enzyme, it is concluded that it should be highly potent in men.

IT **455323-72-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of steroid 5.alpha.-reductase inhibiting acylpiperidines)
RN 455323-72-5 CAPLUS
CN Benzoic acid, 4-[[1-(diphenylacetyl)-4-piperidinyl]oxy]- (9CI) (CA INDEX NAME)



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L14 HAS NO ANSWERS
L14              STR
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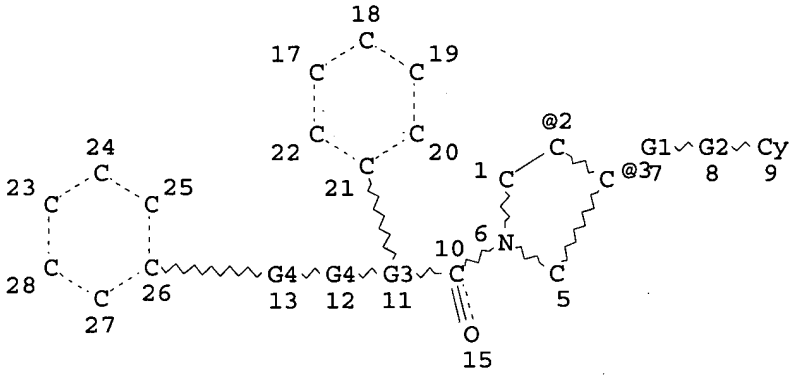


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VAR G2=O/N
VAR G3=C/N
VAR G4=C/O/S/N
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GGCAT   IS MCY  UNS  AT   9
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC  23  21   6
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE


=> s l14 ful
FULL SEARCH INITIATED 15:45:39 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 465221 TO ITERATE

 86.0% PROCESSED  400000 ITERATIONS                                 4 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.21

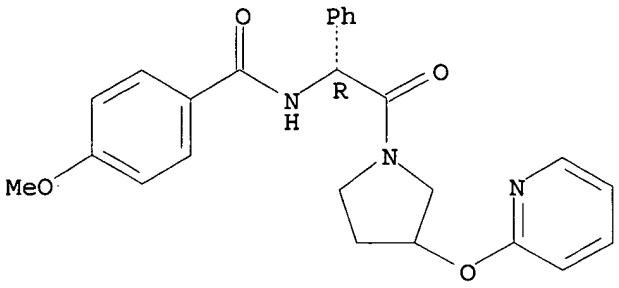
FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       465221 TO   465221
PROJECTED ANSWERS:               4 TO       10

L16            4 SEA SSS FUL L14

=> d 1-4

L16  ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2003 ACS
RN   313488-47-0  REGISTRY
CN   Benzamide, 4-methoxy-N-[(1R)-2-oxo-1-phenyl-2-[3-(2-pyridinyloxy)-1-
     pyrrolidinyl]ethyl]- (9CI)  (CA INDEX NAME)
FS   STEREOSEARCH
MF   C25 H25 N3 O4
SR   CA
LC   STN Files:   CA, CAPLUS

Absolute stereochemistry.
```

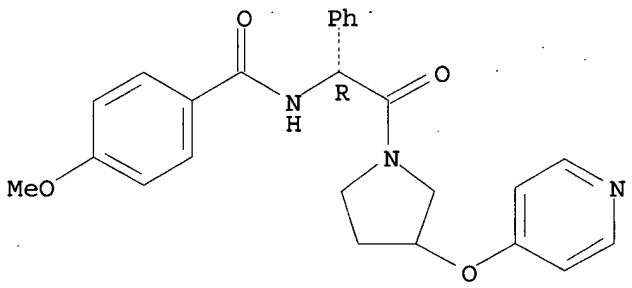


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 313488-44-7 REGISTRY
CN Benzamide, 4-methoxy-N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H25 N3 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

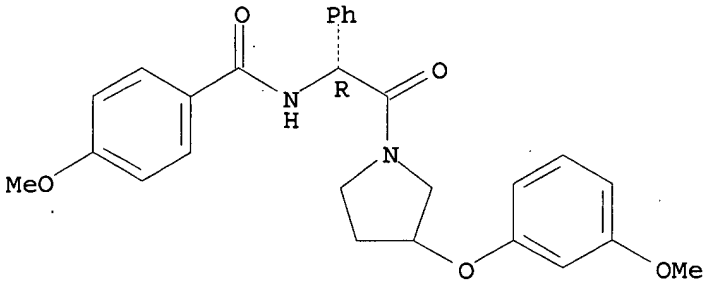


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 313487-90-0 REGISTRY
CN Benzamide, 4-methoxy-N-[(1R)-2-[3-(3-methoxyphenoxy)-1-pyrrolidinyl]-2-oxo-1-phenylethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H28 N2 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

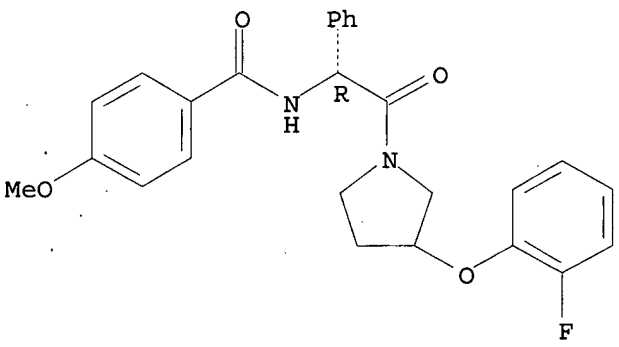


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 313487-89-7 REGISTRY
CN Benzamide, N-[(1R)-2-[3-(2-fluorophenoxy)-1-pyrrolidinyl]-2-oxo-1-phenylethyl]-4-methoxy- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H25 F N2 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



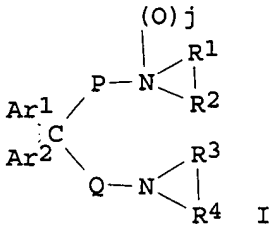
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

AN 2001:228703 CAPLUS
DN 134:252267
TI Preparation of diarylalakanediamine derivatives as melanin concentrating hormone (MCH) antagonists
IN Kato, Kaneyoshi; Mori, Masaaki; Suzuki, Nobuhiro; Shimomura, Yukio; Takekawa, Shiro; Choh, Nobuo
PA Takeda Chemical Industries, Ltd., Japan
SO PCT Int. Appl., 284 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001021169	A1	20010329	WO 2000-JP6376	20000919
	W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000073158	A5	20010424	AU 2000-73158	20000919
	JP 2002097138	A2	20020402	JP 2000-288894	20000919
	EP 1219294	A1	20020703	EP 2000-961076	20000919
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
PRAI	JP 1999-266278	A	19990920		
	JP 2000-221055	A	20000717		
	WO 2000-JP6376	W	20000919		

OS MARPAT 134:252267
GI



I

AB Compds. of general formula [I; wherein Ar1 and Ar2 are each an optionally substituted arom. group; P and Q are each a divalent aliph. hydrocarbon group which may contain ethereal oxygen or sulfur in the carbon chain and may be substituted; R1 and R3 are each (i) hydrogen, (ii) acyl, or (iii) optionally substituted hydrocarbyl; R2 and R4 are each (i) hydrogen, (ii) optionally substituted alkyl, or (iii) optionally substituted alkylcarbonyl; alternatively R1 and R2 or R3 and R4 together with the nitrogen atom adjacent thereto may form a monocyclic or fused nitrogenous heterocyclic group; and j is 0 or 1], salts of the same, or prodrugs thereof are prepd. These compds. are useful for the treatment of diseases caused by MCH, e.g. obesity (as antiobesity agents) or overeating (as appetite depressants), or for the improvement of emotional disorders or sexual function. Thus, benzyl 2-[(5-hydroxy-2,2-diphenylpentyl)amino]-2-oxoethylcarbamate was brominated by Br and Ph3P in MeCN at room temp. for

1 h to give benzyl 2-[(5-bromo-2,2-diphenylpentyl)amino]-2-oxoethylcarbamate which was dissolved in MeCN, treated with 4-phenylpiperidine and K2CO3 in MeCN, and stirred at 40.degree. overnight to give, after purifn. on alumina column chromatog. and conversion into the HCl, benzyl 2-[[2,2-diphenyl-5-(4-phenylpiperidino)pentyl]amino]-2-oxoethylcarbamate hydrochloride (II). II in vitro inhibited the binding of [35S]-guanosine 5'-(.gamma.-thio)triphosphate to human somatostatin-like receptor (SLC-1) with IC50 of 5 nM. Tablet formulations contg. II were described. .

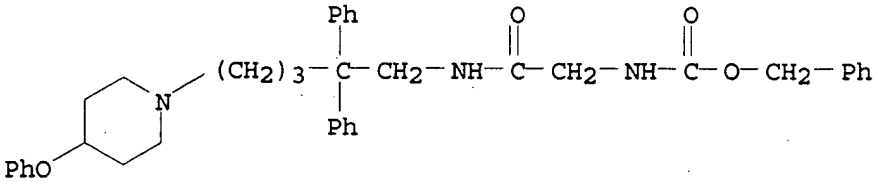
IT **331630-28-5P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of diarylalakanediamine derivs. as melanin concg. hormone (MCH) antagonists for treating MCH-caused diseases)

RN 331630-28-5 CAPLUS

CN Carbamic acid, [2-oxo-2-[[5-(4-phenoxy-1-piperidinyl)-2,2-diphenylpentyl]amino]ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



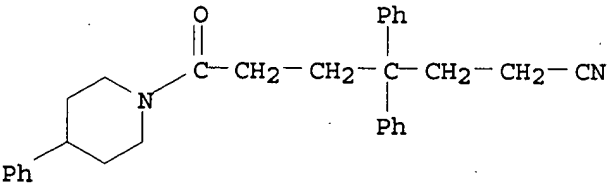
IT **331628-99-0P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of diarylalakanediamine derivs. as melanin concg. hormone (MCH) antagonists for treating MCH-caused diseases)

RN 331628-99-0 CAPLUS

CN Piperidine, 1-(6-cyano-1-oxo-4,4-diphenylhexyl)-4-phenyl- (9CI) (CA INDEX NAME)

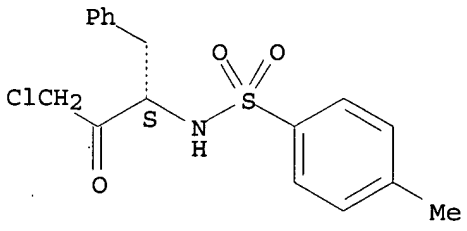


RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 1999:685919 CAPLUS
DN **132:34525**
TI Chloromethyl ketones inhibit interleukin-12 production in mouse macrophages stimulated with lipopolysaccharide
AU Kang, B. Y.; Chung, S. W.; Im, S.-Y.; Hwang, S. Y.; Kim, T. S.
CS College of Pharmacy and Research Institute of Drug Development, Chonnam National University, Kwangju, S. Korea
SO Immunology Letters (1999), 70(2), 135-138
CODEN: IMLED6; ISSN: 0165-2478
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
AB Interleukin-12 (IL-12) plays a pivotal role in the development of T-helper type 1 (Th1) immune response, which may be involved in the pathogenesis of chronic inflammatory autoimmune disorders. In this study, we investigated the effects of N-.alpha.-tosyl-L-phenylalanine chloromethyl ketone (TPCK) and N-.alpha.-tosyl-L-lysine chloromethyl ketone (TLCK), serine protease inhibitors, on the prodn. of IL-12 from macrophages stimulated with lipopolysaccharide (LPS). TPCK and TLCK potently inhibited this LPS-induced IL-12 prodn. in a dose-dependent manner. The effect of TPCK and TLCK on the IL-12 p40 promoter activation was analyzed by transfecting monocytic RAW264.7 cells with p40 promoter-reporter constructs. The repressive effect maps to a region in the p40 promoter contg. a binding site for NF.kappa.B (p40-.kappa.B). A linker scan mutant of the p40-.kappa.B site abrogates the inhibitory effect on the p40 promoter, confirming the functional relevance of the NF.kappa.B site. Our results show that TPCK and TLCK inhibit NF.kappa.B-mediated IL-12 prodn. in macrophages.
IT **37259-58-8**, Serine proteinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; serine proteinase inhibitors inhibit interleukin-12 prodn. in mouse macrophages stimulated with lipopolysaccharide)
RN 37259-58-8 CAPLUS
CN Proteinase, serine (9CI) (CA INDEX NAME)

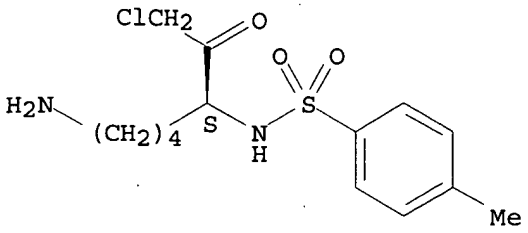
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **402-71-1**, Tpck **2364-87-6**, Tlck
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(serine proteinase inhibitors inhibit interleukin-12 prodn. in mouse macrophages stimulated with lipopolysaccharide)
RN 402-71-1 CAPLUS
CN Benzenesulfonamide, N-[(1S)-3-chloro-2-oxo-1-(phenylmethyl)propyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 2364-87-6 CAPLUS
CN Benzenesulfonamide, N-[(1S)-5-amino-1-(chloroacetyl)pentyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 1986:497950 CAPLUS
DN 105:97950
TI Lysine derivative and proteinase inhibitor
IN Okamoto, Shosuke; Okada, Yoshio; Okunomiya, Akiko; Naito, Taketoshi; Yamada, Morihiko; Kimura, Yoshio; Katsuura, Yasuhiro; Suzuki, Hiroshi; Ohno, Norio; Seki, Yumi
PA Showa Denko K. K., Japan
SO Eur. Pat. Appl., 86 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

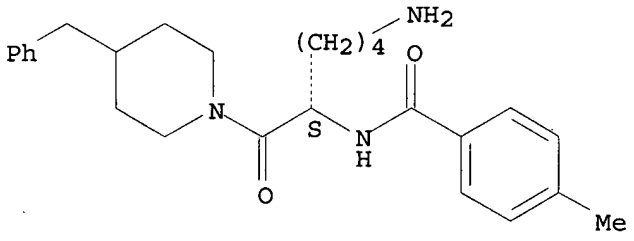
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 183271	A2	19860604	EP 1985-115142	19851129
	EP 183271	A3	19870520		
	EP 183271	B1	19900516		
	R: CH, DE, FR, GB, LI, SE				
	JP 61130268	A2	19860618	JP 1984-251985	19841130
	JP 61189255	A2	19860822	JP 1985-26556	19850215
	JP 61218565	A2	19860929	JP 1985-56153	19850322
	JP 62005945	A2	19870112	JP 1985-143852	19850702
PRAI	JP 1984-251985		19841130		
	JP 1985-26556		19850215		
	JP 1985-56153		19850322		
	JP 1985-143852		19850702		

AB Lysines R1Z1-Lys-R2 (R1 = carbocyclic or heterocyclic aryl; Z1 = SO2, CO; R2 = NH2, substituted amino), which were prepd., showed plasmin inhibition activity. N2-(p-Toluenesulfonyl)-L-lysine 4-benzylpiperidide was prepd. from N6-(benzyloxycarbonyl)lysine in a series of reactions.

IT **103880-75-7P 103880-79-1P 103880-80-4P**
103880-81-5P 103880-82-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as plasmin inhibitor)

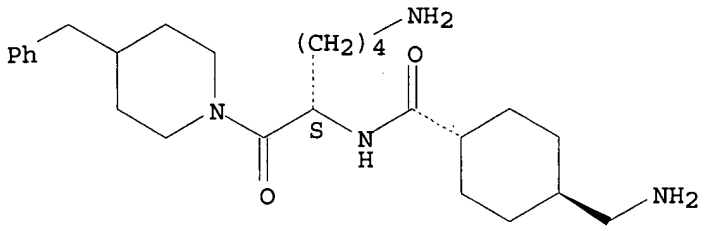
RN 103880-75-7 CAPLUS
CN Benzamide, N-[5-amino-1-[[4-(phenylmethyl)-1-piperidinyl]carbonyl]pentyl]-4-methyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



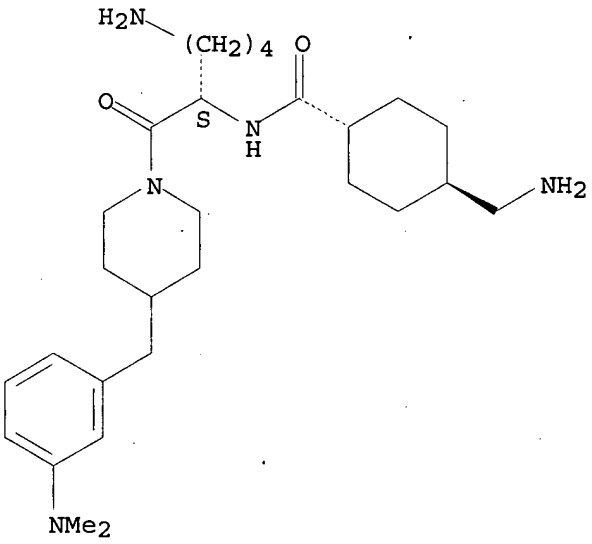
RN 103880-79-1 CAPLUS
CN Cyclohexanecarboxamide, 4-(aminomethyl)-N-[5-amino-1-[[4-(phenylmethyl)-1-piperidinyl]carbonyl]pentyl]-, [1(S)-trans]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

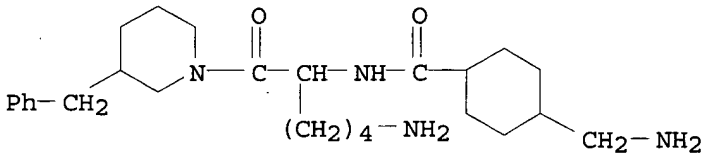


RN 103880-80-4 CAPLUS
CN Cyclohexanecarboxamide, N-[5-amino-1-[[4-[[3-(dimethylamino)phenyl]methyl]-1-piperidinyl]carbonyl]pentyl]-4-(aminomethyl)-, [1(S)-trans]- (9CI) (CA INDEX NAME)

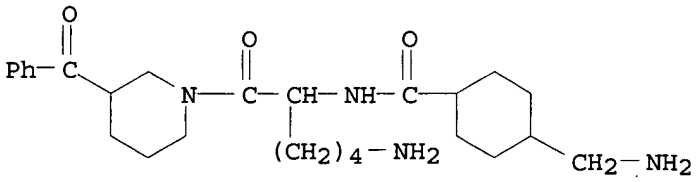
Absolute stereochemistry.



RN 103880-81-5 CAPLUS
CN Cyclohexanecarboxamide, 4-(aminomethyl)-N-[5-amino-1-[[3-(phenylmethyl)-1-piperidinyl]carbonyl]pentyl]- (9CI) (CA INDEX NAME)

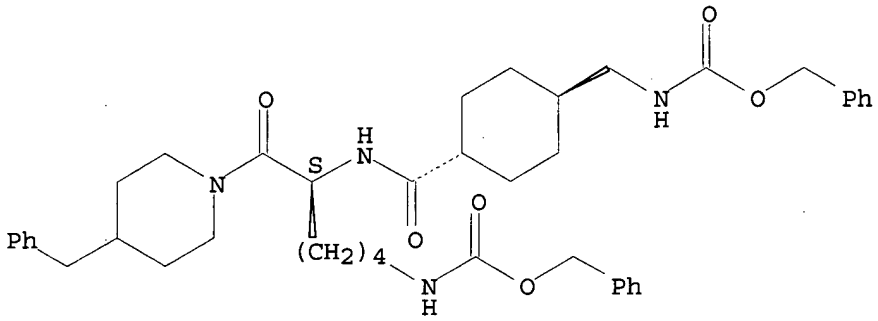


RN 103880-82-6 CAPLUS
CN Cyclohexanecarboxamide, N-[5-amino-1-[(3-benzoyl-1-piperidinyl)carbonyl]pentyl]-4-(aminomethyl)- (9CI) (CA INDEX NAME)



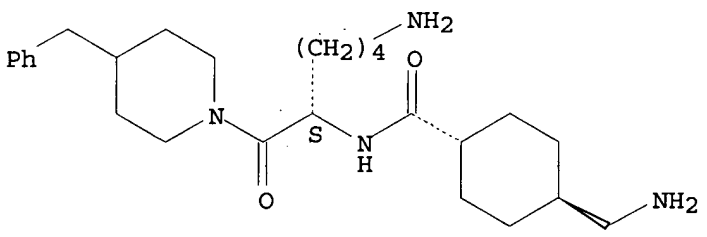
AN 1992:79127 CAPLUS
DN 116:79127
TI Development of active center-directed inhibitors against plasmin
AU Teno, Naoki; Wanaka, Keiko; Okada, Yoshio; Tsuda, Yuko; Okamoto, Utako; Hijikata-Okunomiya, Akiko; Naito, Taketoshi; Okamoto, Shosuke
CS Fac. Pharm. Sci., Kobe-Gakuin Univ., Kobe, 651-21, Japan
SO Chemical & Pharmaceutical Bulletin (**1991**), 39(9), 2340-6
CODEN: CPBTAL; ISSN: 0009-2363
DT Journal
LA English
AB Active center-directed inhibitors of plasmin were designed based on the structure of specific substrates of plasmin and then synthesized. Their effects on plasmin were examd. and the structure-inhibitory activity relationship was studied. N2-trans-4-Aminomethylcyclohexanecarbonyllysine 4-benzoylanilide (Tra-Lys-BZA) inhibited plasmin activities toward S-2251 and fibrin with IC50 values of 15 and 6.1 .mu.M, resp. and N2-trans-4-aminomethylcyclohexanecarbonyllysine 4-benzylpiperidine amide (Tra-Lys-BPP) did not show any detectable inhibitory activity. Moreover, it was revealed that Tra-Lys-4-methoxycarbonylanilide inhibited plasma kallikrein more potently than plasmin.
IT **138848-85-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and deprotection of)
RN 138848-85-8 CAPLUS
CN Carbamic acid, [6-oxo-5-[[[4-[[[(phenylmethoxy)carbonyl]amino]methyl]cyclohexyl]carbonyl]amino]-6-[4-(phenylmethyl)-1-piperidinyl]hexyl]-, phenylmethyl ester, [1(S)-trans]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **103880-79-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and plasmin inhibition by)
RN 103880-79-1 CAPLUS
CN Cyclohexanecarboxamide, 4-(aminomethyl)-N-[5-amino-1-[[4-(phenylmethyl)-1-piperidinyl]carbonyl]pentyl]-, [1(S)-trans]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



c-myc mRNA and up-regulation of c-fos and egr-1 mRNA and protein, which normally occur during TPA-induced differentiation, were not affected by inclusion of the **protease inhibitors**. These data indicate that serine **proteases** specifically mediate many of the phenotypic aspects of TPA-induced monocytic differentiation, but are not involved with the induction or repression of differentiation-sensitive transcription factors, and suggest that **serine protease** activity is required for intracellular processing of CD11b. (c) 2000 Academic Press.

ST **serine protease** role phorbol ester induced HL60 cell differentiation; CD11b processing phorbol ester induced HL60 cell differentiation

L10 ANSWER 4 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1999:685919 CAPLUS
DN 132:34525
TI Chloromethyl ketones inhibit interleukin-12 production in mouse macrophages stimulated with lipopolysaccharide
AU Kang, B. Y.; Chung, S. W.; Im, S.-Y.; Hwang, S. Y.; Kim, T. S.
CS College of Pharmacy and Research Institute of Drug Development, Chonnam National University, Kwangju, S. Korea
SO Immunology Letters (1999), 70(2), 135-138
CODEN: IMLED6; ISSN: 0165-2478
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Interleukin-12 (IL-12) plays a pivotal role in the development of T-helper type 1 (Th1) immune response, which may be involved in the pathogenesis of chronic inflammatory autoimmune disorders. In this study, we investigated the effects of N-.alpha.-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK) and N-.alpha.-tosyl-L-**lysine** chloromethyl ketone (TLCK), **serine protease inhibitors**, on the prodn. of IL-12 from macrophages stimulated with lipopolysaccharide (LPS). TPCK and TLCK potently **inhibited** this LPS-induced IL-12 prodn. in a dose-dependent manner. The effect of TPCK and TLCK on the IL-12 p40 promoter activation was analyzed by transfecting monocytic RAW264.7 cells with p40 promoter-reporter constructs. The repressive effect maps to a region in the p40 promoter contg. a binding site for NF.kappa.B (p40-.kappa.B). A linker scan mutant of the p40-.kappa.B site abrogates the **inhibitory** effect on the p40 promoter, confirming the functional relevance of the NF.kappa.B site. Our results show that TPCK and TLCK **inhibit** NF.kappa.B-mediated IL-12 prodn. in macrophages.

L10 ANSWER 5 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1999:423946 CAPLUS
DN 131:193814
TI **Serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells
AU Huang, Ying; Sheikh, M. Saeed; Fornace, Albert J, Jr.; Holbrook, Nikki J.
CS Gene Expression and Aging Section, Laboratory of Biological Chemistry, National Institute on Aging, Baltimore, MD, 21224, USA
SO Oncogene (1999), 18(23), 3431-3439
CODEN: ONCNES; ISSN: 0950-9232
PB Stockton Press
DT Journal
LA English
RE.CNT 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Serine protease inhibitor** TPCK prevents

Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells

AB The mechanism of Taxol-induced apoptosis was investigated in MCF-7 human breast carcinoma cells. Taxol-induced apoptosis was assocd. with phosphorylation of both c-Raf-1 and Bcl-2 and activation of ERK and JNK MAP kinases. The **serine protease inhibitor** N-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK) effectively blocked apoptosis, but N-p-tosyl-L-**lysine** chloromethyl ketone (TLCK), another **serine protease inhibitor**, was without effect. TPCK treatment also prevented phosphorylation of c-Raf-1 and Bcl-2 in response to Taxol treatment. The **serine protease inhibitor** did not alter JNK activity, but it enhanced Taxol-induced activation of ERK1/2. Treatment of cells with the **inhibitor** of MEK activation, PD98059, prevented Taxol-induced ERK activation both in the presence and absence of TPCK, but did not influence survival of either Taxol- or Taxol plus TPCK-treated cells. In addn., PD98059 had no effect on c-Raf-1 or Bcl-2 phosphorylation. Thus, while the Taxol-induced phosphorylations of c-Raf-1 and Bcl-2 proteins appear to be coupled, these events can be disassocd. from ERK1/2 activation. In summary, these findings suggest that phosphorylation of c-Raf-1 and Bcl-2, but not ERK1/2, are important signaling events in Taxol-induced apoptosis of MCF-7 breast cancer cells and that a TPCK **inhibitable protease**(s) is required for these processes.

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bcl-2; **serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

IT Mammary gland
Mammary gland
(carcinoma, **inhibitors**; **serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

IT Antitumor agents
(mammary gland carcinoma; **serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

IT Apoptosis
Phosphorylation, biological
(**serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

IT 33069-62-4, Taxol
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

IT 139691-76-2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

L10 ANSWER 6 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1999:360059 CAPLUS
DN 131:208734
TI **Inhibition** of drug-induced DNA fragmentation, but not cell death, of glioma cells by non-caspase **protease inhibitors**

AU Eitel, Katrin; Wagenknecht, Bettina; Weller, Michael
CS Department of Neurology, Laboratory of Molecular Neuro-Oncology, School of Medicine, University of Tubingen, Tubingen, 72076, Germany
SO Cancer Letters (Shannon, Ireland) (1999), 142(1), 11-16
CODEN: CALEDQ; ISSN: 0304-3835
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI **Inhibition** of drug-induced DNA fragmentation, but not cell death, of glioma cells by non-caspase **protease inhibitors**
AB The role of non-caspase **protease** activation in drug-induced cell death of glioma cells was examd. Neither calpain **inhibitors** I or II, phenylmethylsulfonyl fluoride (PMSF), N.alpha. -p-tosyl-l-**lysine** chloromethyl ketone (TLCK), N-tosyl-l-**phenylalanine** chloromethyl ketone (TPCK), E64, leupeptin nor pepstatin **inhibit** the cytotoxicity of vincristine, cisplatin, doxorubicin, cytarabine, camptothecin, BCNU or VM26 in two malignant glioma cell lines, T98G and LN-229. However, DNA fragmentation induced by VM26 is **inhibited** by calpain **inhibitor** I, PMSF, TLCK and TPCK, and that induced by camptothecin by calpain **inhibitors** I and II and TPCK. Moreover, **protease inhibitors** fail to abrogate CD95 ligand-induced apoptosis even though DNA fragmentation is attenuated by calpain **inhibitor** II and TPCK. Thus, non-caspase **protease** activation is not required for drug-induced apoptosis of glioma cells. **Protease inhibitor**-mediated **inhibition** of DNA fragmentation operates downstream of the commitment point for cell death.
ST glioma apoptosis **protease inhibitor** antitumor interaction; DNA fragmentation signaling glioma **protease** anticancer
IT DNA
(fragmentation; **inhibition** of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase **protease inhibitors**)
IT Neuroglia
Neuroglia
(glioma, **inhibitors**; **inhibition** of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase **protease inhibitors**)
IT Antitumor agents
(glioma; **inhibition** of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase **protease inhibitors**)
IT Apoptosis
Drug interactions
Signal transduction, biological
(**inhibition** of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase **protease inhibitors**)
IT 78990-62-2, Calpain
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(I and II; **inhibition** of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase **protease inhibitors**)
IT 57-22-7, Vincristine 147-94-4, Cytarabine 154-93-8, BCNU 7689-03-4, Camptothecin 15663-27-1, Cisplatin 23214-92-8, Doxorubicin 29767-20-2, VM26
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(**inhibition** of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase **protease inhibitors**)

IT 329-98-6, Phenylmethylsulfonyl fluoride 402-71-1 2364-87-6 26305-03-3 37259-58-8, **Serine protease** 37353-41-6, Cysteine proteinase 55123-66-5, Leupeptin 66701-25-5, E64 78169-47-8, Aspartic **protease**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**inhibition** of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase **protease inhibitors**)

IT 9001-92-7, **Protease**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(trypsin-like and Chymotrypsin-like; **inhibition** of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase **protease inhibitors**)

L10 ANSWER 7 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1999:158902 CAPLUS
DN 130:294043
TI Inflorescence bud protease(s) against dehydrin-like inflorescence bud proteins of Pistacia vera
AU Peri, Irena; Matusova, Radoslava; Smirnoff, Patricia; Birk, Yehudith; Golan-Goldhirsh, Avi
CS Desert Plant Biotechnology Laboratory, The Jacob Blaustein Institute for Desert Research, The Albert Katz Center for Desert Agrobiology, Ben-Gurion University of the Negev, 84990, Israel
SO Plant Physiology and Biochemistry (Paris) (1999), 37(1), 51-56
CODEN: PPBIEX; ISSN: 0981-9428
PB Editions Scientifiques et Medicales Elsevier
DT Journal
LA English
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB A proteolytic activity extd. from Pistacia vera L. (pistachio) inflorescence buds, found in male and female tissues is reported. The proteolytic activity reaches a peak at the beginning of bud opening and flowering and is directed against inflorescence bud dehydrin-like proteins of pistachio, IBP32 and IBP27. The effect of **protease inhibitors** indicated that the **protease**(s) belong to a **serine-protease**-like family and are not cysteine, acid or metallo-**proteases**. The proteolytic activity was strongly **inhibited** by N.alpha.-p-tosyl-L-**lysine** chloromethyl ketone and to a lesser extent by N-tosyl-L-**phenylalanine** chloromethyl ketone, suggesting mainly trypsin-like specificity or broader **serine-protease** specificity. It is suggested that the proteolytic activity is important in the mobilization of nitrogen reserves stored in the bud storage proteins during dormancy to support the fast-developing inflorescence in spring after bud dormancy break.
IT 37259-58-8, **Serine** proteinase
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(inflorescence bud **protease**(s) against dehydrin-like inflorescence bud proteins of Pistacia vera)

L10 ANSWER 8 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1997:179985 CAPLUS
DN 126:181000
TI Differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents.

[Erratum to document cited in CA125:316457

AU Lotem, Joseph; Sachs, Leo

CS Dep. Mol. Genetics, Weizmann Inst. Sci., Rehovot, 76100, Israel

SO Proceedings of the National Academy of Sciences of the United States of America (1997), 94(4), 1603
CODEN: PNASA6; ISSN: 0027-8424

PB National Academy of Sciences

DT Journal

LA English

TI Differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents. [Erratum to document cited in CA125:316457

AB The authors correct the second sentence of their original abstr. to read as follows. Apoptosis was also suppressed by the **serine** and cysteine **protease inhibitor** N-tosyl-L-**phenylalanine** chloromethylketone (TPCK), but not by other **serine** or cysteine **protease inhibitors** including N.alpha.-p-tosyl-L-**lysine** chloromethylketone (TLCK), E64, pepstatin A, or chymostatin.

ST erratum apoptosis **protease inhibitor** cytokine gene; apoptosis **protease inhibitor** cytokine gene erratum; **protease inhibitor** cytokine gene p53 erratum; cytotoxic agent apoptosis **protease inhibitor** erratum; agent apoptosis **protease inhibitor** cytokine erratum

IT Gene, animal
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(TP53; differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents (Erratum))

IT Apoptosis
Cytotoxic agents
(differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents (Erratum))

IT Interleukin 3
Interleukin 6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents (Erratum))

IT Hematopoietic precursor cell
(myeloid; differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents (Erratum))

IT Thymus gland
(thymocyte; differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents (Erratum))

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma.; differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents (Erratum))

IT 9047-22-7, Cathepsin B 60616-82-2, Cathepsin L 122191-40-6, Interleukin-1.beta.-converting enzyme
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents (Erratum))

IT 50-02-2, Dexamethasone 57-22-7, Vincristine 66-81-9, Cycloheximide 402-71-1 2364-87-6 9076-44-2, Chymostatin 23214-92-8 25013-16-5, BHA 26305-03-3, Pepstatin A 60525-17-9 66701-25-5, E64 83869-56-1, GM-CSF 143180-74-9, Granzyme B 161401-82-7 183284-21-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents (Erratum))

L10 ANSWER 9 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1996:665142 CAPLUS
DN 125:316457
TI Differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents
AU Lotem, Joseph; Sachs, Leo
CS Dep. Mol. Genetics, Weizmann Inst. Sci., Rehovot, 76100, Israel
SO Proceedings of the National Academy of Sciences of the United States of America (1996), 93(22), 12507-12512
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
TI Differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents
AB Apoptosis induced in myeloid leukemic cells by wild-type p53 was suppressed by different cleavage-site directed **protease inhibitors**, which **inhibit** interleukin-1.beta.-converting enzyme-like, granzyme B and cathepsins B and L **proteases**. Apoptosis was also suppressed by the **serine** and cysteine **protease inhibitor** N-tosyl-L-**phenylalanine** chloromethylketone (TPCK), E64, but not by other **serine** or cysteine **protease inhibitors** including N.alpha.-p-tosyl-L-**lysine** chloromethylketone (TLCK), E64, pepstatin A, or chymostatin. **Protease inhibitors** suppressed induction of apoptosis by .gamma.-irradn. and cycloheximide but not by doxorubicin, vincristine, or withdrawal of interleukin 3 from interleukin 3-dependent 32D non-malignant myeloid cells. Induction of apoptosis in normal thymocytes by .gamma.-irradn. or dexamethasone was also suppressed by the cleavage-site directed **protease inhibitors**, but in contrast to the myeloid leukemic cells apoptosis in thymocytes was suppressed by TLCK but not by TPCK. The results indicate that (i) **inhibitors** of interleukin-1.beta.-converting enzyme-like **proteases** and some other **protease inhibitors** suppressed induction of apoptosis by wild-type p53 and certain p53-independent pathways of apoptosis; (ii) the **protease inhibitors** together with the cytokines interleukin 6 and interferon-.gamma. or the antioxidant butylated hydroxyanisole gave a cooperative protection against apoptosis; (iii) these **protease inhibitors** did not suppress induction of apoptosis by some cytotoxic agents or by viability-factor withdrawal from 32D cells, whereas these pathways of apoptosis were suppressed by cytokines; (i.v.) there are cell type differences in the **proteases** involved in apoptosis; and (v) there are multiple pathways leading to apoptosis that can be selectively induced and suppressed by different agents.
ST apoptosis **protease inhibitor** cytokine gene p53; cytotoxic agent apoptosis **protease inhibitor** cytokine
IT Apoptosis
Cytotoxic agents

(differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Gene, animal
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(TP53, differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Lymphokines and Cytokines
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interleukin 3, differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Lymphokines and Cytokines
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interleukin 6, differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Hematopoietic precursor cell
(myeloid, differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Thymus gland
(thymocyte, differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma., differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT 9047-22-7, Cathepsin B 60616-82-2, Cathepsin L 122191-40-6, Interleukin-1.beta.-converting enzyme
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT 50-02-2, Dexamethasone 57-22-7, Vincristine 66-81-9, Cycloheximide 402-71-1 2364-87-6, N.alpha.-p-Tosyl-L-lysine chloromethylketone 9076-44-2, Chymostatin 23214-92-8, Doxorubicin 25013-16-5, BHA 26305-03-3, Pepstatin A 60525-17-9 66701-25-5, E64 83869-56-1, GM-CSF 143180-74-9, Granzyme B 161401-82-7 183284-21-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

L10 ANSWER 10 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1996:482438 CAPLUS
DN 125:163645
TI Partial characterization of protease activity in the midgut of Helicoverpa armigera larvae

AU Wang, Chenzhu; Qin, Junde
CS Institute Zoology, Academia Sinica, Beijing, 100080, Peop. Rep. China
SO Kunchong Xuebao (1996), 39(1), 7-14
CODEN: KCHPA2; ISSN: 0454-6296
PB Kexue
DT Journal
LA Chinese
AB The activities of three serine **proteases** in the midgut of Helicoverpa armigera larvae were partially characterized. The enzymes were an active alk. trypsin-like enzyme with maximal hydrolysis of benzoyl arginine p-nitroaniline at pH 10.50 or higher; a weak alk. trypsin-like enzyme with maximal hydrolysis of tosyl-L-arginine Me ester at pH 8.50-9.00; and a chymotrypsin-like enzyme with maximal hydrolysis of benzoyl-L-tyrosine Et ester at pH 8.50-9.00. Total proteolysis, measured by using azocasein, had a maximal activity at pH 10.50 or higher. Ca2+ had no activation effect on larval **proteases**, but Mg2+ activated the weak alk. trypsin-like enzyme. The **inhibition** with Ph Me sulfonyl fluoride and tosyl-L-**lysine** chloromethyl ketone to the weak alk. trypsin-like enzyme activity was greater than that to the active alk. trypsin-like enzyme activity. The tosyl-L-**phenylalanine** chloromethyl ketone was not only the **inhibitor** of the chymotrypsin-like enzyme, but also the activator of the weak alk. trypsin-like enzyme. Comparison between the insect **protease** and bovine counterpart **protease** revealed difference in **inhibitor** sensitivity.
ST Helicoverpa armigera **protease** activator **inhibitor**
IT Heliothis zea
(serine **proteases** of midgut of Helicoverpa armigera larvae response to soybean trypsin **inhibitor**)
IT Digestive tract
(midgut, serine **proteases** of midgut of Helicoverpa armigera larvae response to soybean trypsin **inhibitor**)
IT 9002-07-7, Trypsin 9004-07-3, Chymotrypsin 37259-58-8, **Serine protease**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(**serine** proteases of midgut of Helicoverpa armigera larvae)
IT 9078-38-0, Soybean trypsin **inhibitor**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(serine **proteases** of midgut of Helicoverpa armigera larvae response to soybean trypsin **inhibitor**)

L10 ANSWER 11 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1996:277183 CAPLUS
DN 124:335473
TI Antiproteases attenuate the release of neutrophil chemotactic activity from bronchial epithelial cells induced by smoke
AU Koyama, Sekiya; Rennard, Stephen I.; Leikauf, George D.; Ertl, Ronald F.; Robbins, Richard A.
CS School Medicine, Shinshu University, Matsumoto, Japan
SO Experimental Lung Research (1996), 22(1), 1-19
CODEN: EXLRDA; ISSN: 0190-2148
PB Taylor & Francis
DT Journal
LA English
AB The released neutrophil chemotactic activity (NCA) from bronchial epithelial cells (BECs) in response to smoke ext. was evaluated by reverse-phase, high-performance liq. chromatog. (RP-HPLC) and the involvement of proteolytic activity was assessed for the release of NCA from BECs. Smoke ext. stimulated the release of NCA (55.3 .+-. 5.2 us. 17.3 .+-. 4.1 cells per high-power field [HPF], p<.001). The released activity detd. by RP-HPLC anal. was 15-hydroxyeicosatetraenoic acid and

leukotriene B4. Several structurally and functionally different **serine protease inhibitors**, including .alpha.-1-**protease inhibitor** (.alpha.-1-PI), chloromethyl ketone (CK) derivs., N-tosyl-L-**lysine** CK (TLCK), methoxysuccinyl-Ala-Ala-Pro-Val CK (SPCK), N-.alpha.-tosyl-L-**phenylalanine** CK (TPCK), and N-.alpha.-p-tosyl-L-arginine Me ester hydrochloride (TAME), attenuated the release of NCA ($p < .01$) in a dose-dependent fashion. Leupeptin, a cysteine **protease inhibitor**, has only a small effect on the release of NCA ($p < .05$), and phosphoramidon, a neutral endopeptidase **inhibitor**, had no effect. The measurement of proteolytic enzyme activity using synthetic substrate S-2288 revealed that smoke ext. significantly ($p < .05$) augmented the **serine protease** activity in BEC layers. Culture supernatant fluids and cell lysates of BECs in response to smoke ext. solubilized 14C-labeled casein. These results suggest that BECs may release lipoxygenase-derived NCA in response to smoke ext. and that the release of NCA may involve the activation of proteolytic activity of BECs which was **inhibited** by **serine protease inhibitors**.

IT 37259-58-8, **Serine protease** 71160-24-2, Leukotriene B4 73180-00-4, 15-Hydroxyeicosatetraenoic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effect of cigarette smoke on neutrophil chemotactic activity and proteases of bronchial epithelial cells)

L10 ANSWER 12 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1996:153397 CAPLUS
DN 124:203102
TI Preparation of peptide containing proline phosphonate derivatives as **inhibitors** of serine **proteases**
IN Powers, James C.; Boduszek, Bogdan; Oleksyszyn, Jozef
PA Georgia Tech. Research Corp., USA
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9529691	A1	19951109	WO 1995-US5345	19950428
	W: CA, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5543396	A	19960806	US 1994-234181	19940428
PRAI	US 1994-234181		19940428		

OS MARPAT 124:203102
TI Preparation of peptide containing proline phosphonate derivatives as **inhibitors** of serine **proteases**
AB Peptidyl derivs. of diesters of .alpha.-aminoalkylphosphonic acids, particularly those with proline or related structures, [I and II; Z, Z1 = C1-6 perfluoroalkyl, (un)substituted Ph; X = a single bond, CH2, CH2CH2, (CH2)3, (CH2)4, Y, CH2Y, YCH2, (H,H); Y = O, S; AA = H, PhCH2O2C, H2NCHRCO (wherein R = C1-6 alkyl optionally fluorinated), .beta.-alanine, glycine, .epsilon.-aminocaproic acid, sarcosine, side chain (un)blocked L-, D-, or DL-.alpha.-amino acid selected from the group consisting of alanine, leucine, isoleucine, proline, methionine, methionine sulfoxide, **phenylalanine**, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, **lysine**, arginine, histidine, phenylglycine, and etc.], useful for **inhibiting** serine **proteases** with chymotrypsin-like, trypsin-like, elastase-like, and dipeptidyl peptidase IV specificity and their roles as anti-inflammatory agents, anticoagulants, anti-tumor agents, and anti-AIDS agents, are prepd. Thus, to 0.36 g Boc-D-Phe-Pro-OH

in 2 mL dry DMF at 0.degree., 0.17 g N,N'-dicyclohexylcarbodiimide was added. After stirring the mixt. for 1 h, 0.45 g di-Ph amino(4-amidinophenyl)methanephosphonate dihydrochloride was added the soln. was stirred for 48 h to give di-Ph N-(N-tert-butoxycarbonyl-D-phenylalanyl-L-prolyl)amino(4-amidinophenyl)methanephosphonate hydrochloride. H-Ala-ProP(OC6H4Cl-4)2.HCl and H-Ala-PipP(OC6H4Cl-4)2.HCl in vitro at 0.12 mM **inhibited** human placenta dipeptidylpeptidase IV (DPP-IV) at 0 and 88% after 2 min, resp., and 88 and 100%, resp., after 30 min.

ST peptide phosphonate prepn **inhibitor serine protease**; proline phosphonate contg peptide prepn; antiinflammatory peptide phosphonate; anticoagulant peptide phosphonate; antitumor peptide phosphonate; AIDS treatment peptide phosphonate; dipeptidylpeptidase IV **inhibitor**; aminoalkylphosphonate ester peptide **serine protease inhibitor**

IT Inflammation **inhibitors**
Neoplasm **inhibitors**
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of serine **proteases** for therapeutics)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of serine **proteases** for therapeutics)

IT Acquired immune deficiency syndrome
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of serine **proteases** for treating AIDS)

IT 82818-44-8P 122299-42-7P 122299-43-8P 122299-44-9P 130699-14-8P
130699-15-9P 130699-16-0P 130699-22-8P 130727-19-4P 130727-20-7P
130727-21-8P 140668-71-9P 174298-04-5P 174298-05-6P 174298-06-7P
174298-07-8P 174298-08-9P 174298-09-0P 174298-10-3P 174298-11-4P
174298-12-5P 174298-13-6P 174298-14-7P 174298-15-8P 174298-16-9P
174298-17-0P 174298-18-1P 174298-19-2P 174298-20-5P 174298-21-6P
174298-22-7P 174298-23-8P 174298-25-0P 174298-26-1P 174298-27-2P
174298-28-3P 174298-29-4P 174298-30-7P 174298-31-8P 174298-32-9P
174298-33-0P 174298-34-1P 174298-35-2P 174298-36-3P 174298-37-4P
174298-38-5P 174298-39-6P 174298-40-9P 174298-41-0P 174298-42-1P
174298-43-2P 174391-77-6P 174391-78-7P 174391-79-8P 174391-80-1P
174391-81-2P 174391-82-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of serine **proteases** for therapeutics)

IT 37259-58-8, **Serine protease** 54249-88-6, Dipeptidylpeptidase IV
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of **serine proteases** for therapeutics)

IT 75-89-8, 2,2,2-Trifluoroethanol 78-84-2, Isobutyraldehyde 101-02-0, Triphenyl phosphite 105-07-7, 4-Cyanobenzaldehyde 106-48-9, 4-Chlorophenol 371-41-5, 4-Fluorophenol 405-39-0 621-84-1, Benzyl carbamate 1142-20-7 1148-11-4 1149-26-4 1161-13-3 4712-55-4, Diphenyl phosphite 7719-12-2, Phosphorus trichloride 13734-41-3 16012-70-7 18942-49-9 27879-53-4, 2,3,4,5-Tetrahydropyridine trimer 38675-10-4 54564-48-6, 1-Pyrroline trimer 65164-80-9 72252-95-0 73270-42-5 73270-43-6 73270-44-7 92740-48-2 130727-23-0 174298-44-3 174298-47-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of peptide contg. proline phosphonate derivs. as

inhibitors of serine **proteases** for therapeutics)

IT 98-88-4P, Benzoyl chloride 350-71-0P 5679-61-8P 15516-41-3P 65475-25-4P 152904-82-0P 174298-45-4P 174298-46-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of serine **proteases** for therapeutics)

L10 ANSWER 13 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1995:499553 CAPLUS
DN 123:50579
TI Myosin heavy chain-degrading proteinase from spear squid muscle
AU Ebina, Hiizu; Nagashima, Yuji; Ishizaki, Shoichiro; Taguchi, Takeshi
CS Department of Food Science and Technology, Tokyo University of Fisheries, Tokyo, 108, Japan
SO Food Research International (1995), 28(1), 31-6
CODEN: FORIEU; ISSN: 0963-9969
PB Elsevier
DT Journal
LA English
AB A trypsin-like proteinase responsible for textural deterioration of thermally induced gel was purified to apparent homogeneity from spear squid Loligo bleekeri mantle muscle by chromatog. on Sephacryl S-400 and DEAE Sepharose. The enzyme gave a protein band with a mol. wt. of 42 kDa on SDS-PAGE. The proteinase readily hydrolyzed casein, synthetic peptide butyloxycarbonyl-valine-leucine-**lysine**-4-methylcoumaryl-7-amide (Boc-Val-Leu-Lys-MCA) and myosin heavy chain. The proteolytic activity was effectively **inhibited** by **serine protease inhibitors** such as soybean trypsin **inhibitor** and N.alpha.-p-tosyl-L-**lysine**-chloromethyl ketone, but was not affected by the other types of **protease inhibitors** (e.g., EDTA, EGTA, iodoacetic acid, mercuric chloride and N-tosyl-L-**phenylalanine**-chloromethyl ketone). The optimal temp. was 40.degree. for hydrolysis of both casein and Boc-Val-Leu-Lys-MCA. The optimal pH values were 6.8 and 7.9 for the caseinolytic and peptide-hydrolyzing activity, resp. The proteolytic activity was increased 1.3-fold by addn. of 0.25M NaCl, but not by the addn. of Ca2+. Myosin heavy chain was shown to be cleaved into smaller fragments by incubation with the proteinase on SDS-PAGE. These results revealed that the enzyme was involved in degrdn. of myosin heavy chain from the squid mantle meat.

L10 ANSWER 14 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1995:440581 CAPLUS
DN 122:259635
TI NS3-4A of hepatitis C virus is a chymotrypsin-like protease
AU Hahm, Bumsuk; Han, Dae Sung; Back, Sung Hoon; Song, Ok-Kyu; Cho, Myung-Jae; Kim, Chul-Joong; Shimotohno, Kunitada; Jang, Sung Key
CS Department Life Science, Pohang University Science Technology, Pohang, 790-784, Japan
SO Journal of Virology (1995), 69(4), 2534-9
CODEN: JOVIAM; ISSN: 0022-538X
PB American Society for Microbiology
DT Journal
LA English
AB The polyprotein encoded by a single open reading frame of hepatitis C virus (HCV) is processed by host- and virus-encoded **proteases**. The viral **protease** NS3 is responsible for the cleavage of at least four sites (NS3/4A, NS4A/4B, NS4B/5A, and NS5A/5B junctions) in the nonstructural protein region. To characterize the **protease** function of NS3 and NS4 on various target sites, efficient cis- and trans-cleavage assay systems were developed by using in vitro transcription and translation. Deletion of the C-terminal two-thirds from

NS3 in an NS3-NS4A-4B polypeptide (NS3.DELTA.C-4A-4B) hampered cleavage of the NS3/4A junction but not that of the NS4A/4B junction. As a consequence, expression of NS3.DELTA.C-4A-4B contg. an internal deletion of NS3 results in an NS3.DELTA.C-4A fusion protein. NS3.DELTA.C-4A shows very efficient and specific trans-cleavage activity at NS4A/4B, NS4B/5A, and NS5A/5B junctions. In addn., the biochem. properties of HCV NS3.DELTA.C-4A were further elucidated by adding known **protease inhibitors** in trans-cleavage reactions. The HCV **protease** NS3-4A is **inhibited** by chymotrypsin-specific **inhibitors** N-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK), chymostatin, and Pefabloc SC but not by trypsin-like **protease inhibitors** antipain, leupeptin, and N-.alpha.-p-tosyl-L-**lysine** chloromethyl ketone (TLCK) or by the **protease inhibitors** E-64, bestatin, pepstatin, and phosphoramidon. This finding strongly suggests that HCV **protease** NS3-4A is a chymotrypsin-like **serine protease**.

L10 ANSWER 15 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1995:12109 CAPLUS
DN 122:26398
TI Characterization of three neutral proteases of Spirometra mansoni plerocercoid
AU Kong, Y.; Chung, Y. -B.; Cho, S. -Y.; Choi, S. -H.; Kang, S. -Y.
CS Coll. Med., Chung-Ang Univ., Seoul, 156-756, S. Korea
SO Parasitology (1994), 108(3), 359-68
CODEN: PARAAE; ISSN: 0031-1820
DT Journal
LA English
AB In the pathogenesis of sparganosis, **proteases** have been considered to play important roles in tissue migration and parasite feeding. Several bands of proteolysis were obsd. when crude exts. of Spirometra mansoni plerocercoid (sparganum) were examd. using gelatin substrate gel at neutral pH, of which two **proteases** of 198 and 104 kDa were purified by two chromatog. steps, and a 36 kDa **protease** was purified by gelatin-affinity and DEAE-anion exchange chromatog. All the purified **proteases** exhibited optimal activity at pH 7.5 and 0.1 M Tris-HCl. Proteolytic activities at 198 and 104 kDa were **inhibited** specifically by **serine protease inhibitors**, and 4-(amidinophenyl)methansulfonyl fluoride (APMSF, 0.5 mM) and N-.alpha.-p-tosyl-L-**lysine** chloromethyl ketone (TLCK, 1 mM), which strongly suggested that these two **proteases** were trypsin-like **proteases**. The activity of the 36 kDa **protease** was **inhibited** by N-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK, 1 mM), and chymostatin (0.1 mM), and was potentiated in 10 mM Ca2+ which showed that the **protease** had a chymotrypsin-like property. All the **proteases** were Schiff (PAS) pos. **Proteases** of 198 and 104 kDa degraded collagen completely within 24 h. The 36 kDa enzyme cleaved human recombinant interferon-.gamma. (rIFN.gamma.) and bovine myelin basic protein. In addn., all the purified proteins elicited strong antibody responses in the infected patients.

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     (FILE 'HOME' ENTERED AT 11:06:39 ON 20 JUN 2003)

     FILE 'CAPLUS' ENTERED AT 11:06:44 ON 20 JUN 2003
L1         38789 S PROTEAS?(L)INHIBIT?
L2           116 S L1 (L)(LYSINE(L)PHENYLALANINE)
L3            66 S L2 AND (LYSINE(10A)PHENYLALANINE)
L4            58 S L3 AND PY<1999
L5             1 S L4 AND P/DT
L6            57 S L4 NOT L5
L7            20 S L6 AND (SERINE(10A)PROTEASE)

=> l1 and (serine(10a)protease)
L1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l1 and (serine(10a)protease)
          89713 SERINE
          75675 PROTEASE
           9624 SERINE(10A)PROTEASE
L8         5755 L1 AND (SERINE(10A)PROTEASE)

=> s l8 and (lysine(l)phenylalanine)
          90278 LYSINE
          67940 PHENYLALANINE
           9090 LYSINE(L)PHENYLALANINE
L9           49 L8 AND (LYSINE(L)PHENYLALANINE)

=> s l9 not l7
L10          29 L9 NOT L7

=> d bib hit 16-29

L10  ANSWER 16 OF 29  CAPLUS  COPYRIGHT 2003 ACS
AN   1993:226008  CAPLUS
DN   118:226008
TI   The detection and isolation of protease activity associated with purified
     preparations of human chorionic gonadotropin
AU   Daja, Mirella M.; Hiyama, Jun; Scott, G. Kenneth; Renwick, Alistair G. C.
CS   Dep. Biochem., Univ. Auckland, Auckland, N. Z.
SO   Endocrinology (1993), 132(4), 1766-73
     CODEN: ENDOAO; ISSN: 0013-7227
DT   Journal
LA   English
AB   The highly purified human chorionic gonadotropin (hCG) CR series is widely
     used as a ref. material in immunol. and biol. assays.  However, these
     hormone prepns., specifically hCG (CR127), exhibit Arg-specific peptidase
     activity with synthetic peptide substrates.  The putative serine
     protease-like activity assocd. with hCG (CR127) was almost
     completely inhibited by diisopropylfluorophosphate, soybean
     trypsin inhibitor, N-tosyl-L-phenylalanine
     chloromethyl ketone and to a lesser extent by N-.alpha.-p-tosyl-L-
     lysine chloromethyl ketone and was isolated after hydrophobic
     interaction and affinity chromatog. with soybean trypsin inhibitor
     , which indicated the presence of exogenous protease
     contaminants rather than intrinsic peptidase activity.  [3H]-DFP labeling
     and SDS-PAGE of the isolated contaminants revealed 2 possible serine
     proteases of apparent mol. wts. 60,000 and 20,000.  The presence
     of these contaminants had no apparent effect on the receptor binding
     capability of hCG; however, the in vitro biol. activity of hCG detd. by
     maximal cAMP prodn. was decreased after hydrophobic interaction chromatog.
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purifn. of the hormone. These observations suggest that the **serine protease**-like contaminants enhance cAMP prodn., thereby introducing a significant source of error in biol. assays that use hCG (CR127). Further purifn. of hCG by hydrophobic interaction and affinity chromatog. is recommended before its use in bioassays or research.

ST chorionic gonadotropin prepn **serin protease** contamination

IT Receptors
RL: SPN (Synthetic preparation); PREP (Preparation)
(gonadotropin, chorionic gonadotropin binding by, **serine protease** contamination of purified prepns. in relation to)

IT Gonadotropins
RL: SPN (Synthetic preparation); PREP (Preparation)
(receptors, chorionic gonadotropin binding by, **serine protease** contamination of purified prepns. in relation to)

IT 37259-58-8, **Serine protease**
RL: BIOL (Biological study)
(chorionic gonadotropin from human purified prepns. contamination by, detection and isolation of)

IT 60-92-4, CAMP
RL: FORM (Formation, nonpreparative)
(formation of, chorionic gonadotropin stimulation of, **serine protease** contamination of purified prepns. enhancement of)

IT 9002-61-3, Chorionic gonadotropin
RL: BIOL (Biological study)
(**serine protease** contamination of purified prepns. of human, detection and isolation of)

L10 ANSWER 17 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1991:202438 CAPLUS
DN 114:202438
TI Site-directed mutagenesis of alanine-382 of human antithrombin III
AU Austin, Richard C.; Rachubinski, Richard A.; Blajchman, Morris A.
CS Canad. Red Cross Blood Transfus. Serv., Hamilton, ON, L3N 3Z5, Can.
SO FEBS Letters (1991), 280(2), 254-8
CODEN: FEBLAL; ISSN: 0014-5793
DT Journal
LA English
AB Antithrombin III Hamilton is a structural variant of antithrombin III (AT-III) with normal heparin affinity but impaired **serine protease inhibitory** activity. The mol. defect of AT-III-Hamilton is a substitution of threonine for alanine at amino acid residue 382. Recently it has been shown that both plasma-derived and cell-free-derived AT-III-Hamilton polypeptides act as substrates rather than **inhibitors** of thrombin and factor Xa. In the present study, the cell-free expression phagemid vector pGEM-3Zf(+)-AT-III1-432 was mutated at amino acid residue 382 of AT-III to generate 7 cell-free-derived variants. All these cell-free-derived AT-III variants were able to bind heparin as effectively as cell-free-derived normal AT-III. In terms of .alpha.-thrombin **inhibitory** activity each variant reacted differently. Variants could be grouped into 3 categories with respect to thrombin-AT-III complex formation: (1) near normal activity (glycine, isoleucine, leucine, valine); (2) low activity (threonine, glutamine); (3) no detectable activity (**lysine**). These data suggest that mutations at position 382 of AT-III may have a variable effect on **protease inhibitory** activity, depending on either the stability of the P12-P9 region of the exposed loop of AT-III, or the inability of the amino acid residue at position 382 to interact with a conserved hydrophobic pocket consisting of **phenylalanine** (at positions 77, 221 and 422) and isoleucine (position 412) residues.

L10 ANSWER 18 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1991:141238 CAPLUS
DN 114:141238
TI Influence of **protease** on **inhibitory** and stimulatory effects of interleukin 1.beta. on .beta.-cell function
AU Welsh, Nils; Bendtzen, Klaus; Sandler, Stellan
CS Dep. Med. Cell Biol., Uppsala Univ., Uppsala, S-751 23, Swed.
SO Diabetes (1991), 40(2), 290-4
CODEN: DIAEAZ; ISSN: 0012-1797
DT Journal
LA English
TI Influence of **protease** on **inhibitory** and stimulatory effects of interleukin 1.beta. on .beta.-cell function
AB To elucidate the putative role of **proteases** in the action of interleukin 1.beta. (IL-1.beta.) on pancreatic .beta.-cells, the authors studied the effects on islet function of different **protease inhibitors** when added together with recombinant IL-1.beta. to isolated rat pancreatic islets. The trypsin **inhibitor** n.alpha.-p-tosyl-L-**lysine** chloromethyl ketone (TLCK) counteracted the acute stimulatory effects of IL-1.beta. on islet glucose oxidn., insulin release, and biosynthesis. TLCK also partially or completely counteracted the long-term **inhibitory** effects of IL-1.beta. on islet glucose oxidn., insulin biosynthesis, content, and release. This **protease inhibitor** also counteracted IL-1.beta.-induced .beta.-cell cytotoxicity as assessed by DNA content measurements. Of the other group-specific **protease inhibitors** investigated, only n-tosyl-L-**phenylalanine** chloromethyl ketone, n.alpha.-p=tosyl-L-arginine Me ester, and chloromercuriphenylsulfonic acid were found to partially protect against IL-1.beta. action. It is concluded that **protease** activation, putatively a **serine protease**, may be an early and perhaps primary event in the action of IL-1.beta. on .beta.-cells.
IT 402-71-1 901-47-3 2364-87-6, N.alpha.-p-Tosyl-L-lysine chloromethyl ketone
RL: BIOL (Biological study)
(interleukin 1.beta. effect on pancreatic .beta. cells **inhibition** by, **protease** in relation to)
IT 37259-58-8, **Serine protease**
RL: BIOL (Biological study)
(interleukin 1.beta. effect on pancreatic .beta.-cells in relation to)

L10 ANSWER 19 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1990:478910 CAPLUS
DN 113:78910
TI Synthesis of new phosphonate **inhibitors** of serine **proteases**
AU Fastrez, Jacques; Jespers, Laurent; Lison, Dominique; Renard, Michel; Sonveaux, Etienne
CS Louvain-la-Neuve, B-1348, Belg.
SO Tetrahedron Letters (1989), 30(49), 6861-4
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 113:78910
TI Synthesis of new phosphonate **inhibitors** of serine **proteases**
AB Phosphonate inhibitors AcNHCHRP(O)(OR1)OC6H4Cl-3 [I, R = CH2Ph, (CH2)4NH2; R1 = Et, 3-ClC6H4] were prepd. as analogs of **phenylalanine** and **lysine** esters. The inhibitory powers of I were tested in vitro on chymotrypsin, trypsin, and urokinase.
ST acetylphenylalanine phosphonate analog chymotrypsin **inhibitor**; trypsin **inhibitor** acetyllysine phosphonate analog; urokinase **inhibitor** acetyllysine phosphonate analog; **serine**

protease inhibitor acetylaminophosphonate prepn
IT 37259-58-8, **Serine protease**
RL: PROC (Process)
(**inhibition** of, with acetylphenylalanine and acetyllysine phosphonate analogs)

L10 ANSWER 20 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1989:453055 CAPLUS
DN 111:53055
TI Novel **inhibitors** of human leukocyte elastase and cathepsin G. Sequence variants of squash seed **protease inhibitor** with altered **protease** selectivity
AU McWherter, Charles A.; Walkenhorst, William F.; Campbell, Edward J.; Glover, George I.
CS Dep. Biol. Sci., Monsanto Co., St. Louis, MO, 63198, USA
SO Biochemistry (1989), 28(14), 5708-14
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
TI Novel **inhibitors** of human leukocyte elastase and cathepsin G. Sequence variants of squash seed **protease inhibitor** with altered **protease** selectivity
AB Novel peptide inhibitors of human leukocyte elastase (HLE) and cathepsin G (CG) were prepd. by solid-phase peptide synthesis of P1 amino acid sequence variants of Curcurbita maxima trypsin inhibitor III (CMTI-III), a 29-residue peptide found in squash seeds. A systematic study of P1 variants indicated that P1 arginine, **lysine**, leucine (Leu), alanine (Ala), **phenylalanine** (Phe), and methionine (Met) inhibited trypsin; P1 valine (Val), isoleucine (Ile), glycine (Gly), Leu, Ala, Phe, and Met inhibited HLE; P1 Leu, Ala, Phe, and Met inhibited CG and chymotrypsin. Variants with P1 Val, Ile, or Gly were selective inhibitors of HLE, whereas inhibition of trypsin required P1 amino acids with an unbranched .beta.-C atom. Studies of Val-5-CMTI-III (P1 Val) inhibition of HLE demonstrated a 1:1 binding stoichiometry with an apparent Ki of 8.7 nM. The inhibition of HLE by Gly-5-CMTI-III indicated a significant role for reactive-site structural moieties other than the P1 side-chain. Val-5-CMTI-III inhibited both HLE and human polymorphonuclear leukocyte (PMN) proteolysis of surface-bound 125I-labeled fibronectin. Val-5-CMTI-III was more effective at preventing turnover of a peptide p-nitroanilide substrate than halting the dissoln. of 125I-labeled fibronectin. It was about as effective as human serum .alpha.1-proteinase inhibitor in preventing PMN degrdn. of the connective tissue substrate. In addn. to providing interesting candidates for controlling inflammatory cell proteolytic injury, the CMTI-based inhibitors are ideal for studying mol. recognition because of their small size, their ease of prepn., and the availability of sensitive and quant. assays for intermol. interactions.
ST **protease inhibitor** squash peptide analog prepn; trypsin **inhibitor** squash peptide analog prepn; elastase **inhibition** squash trypsin **inhibitor** analog; cathepsin G **inhibition** trypsin **inhibitor** analog; inflammation proteolytic injury **inhibition** peptide squash
IT 9002-07-7, Trypsin 9004-07-3, Chymotrypsin 37259-58-8, **Serine protease**
RL: PROC (Process)
(**inhibition** of, by analogs of trypsin **inhibitor** III of squash seeds)

L10 ANSWER 21 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1989:227593 CAPLUS
DN 110:227593
TI Kinetics and specificity of serine proteases in peptide synthesis catalyzed in organic solvents

AU Gaertner, Hubert; Puigserver, Antoine
CS Cent. Biochem. Biol. Mol., Marseille, F-13402, Fr.
SO European Journal of Biochemistry (1989), 181(1), 207-13
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB Initial rates of peptide-bond synthesis catalyzed by poly(ethylene glycol)-modified chymotrypsin in benzene were detd. using HPLC. Enzymic synthesis of N-benzoyl-L-tyrosyl-L-**phenylalanine** amide from N-benzoyl-L-tyrosine Et ester and L-**phenylalanine** amide was found to obey Michaelis-Menten kinetics and to be consistent with a ping-pong mechanism modified by a hydrolytic branch. The catalytic activity of modified chymotrypsin was dependent on both concn. and type of org. solvent, the highest synthesis rate being obtained in toluene. Since the chymotrypsin specificity in the org. phase was actually altered, the enzyme's apparent kinetic parameters were detd. for differential substrates and compared to those obtained with other serine **proteases** in benzene. Both N-benzoyl-L-tyrosine Et ester and N-.alpha.-benzoyl-L-**lysine** Me ester were comparable acyl donors in benzene and the (kcat/Km)app value of modified chymotrypsin was only 10-fold smaller than that obtained with poly(ethylene glycol)-modified trypsin in the synthesis of N-.alpha.-benzoyl-L-lysyl-L-**phenylalanine** amide. The change in chymotrypsin specificity was also confirmed through the binding of trypsin **inhibitors** in benzene. The overall results suggest that hydrophobic bonding between the enzyme and its substrate should not be taken into account during catalysis in the org. phase. In general, if hydrophobic interactions are involved in the binding of substrates to the active site in aq. media, the replacement of water by hydrophobic solvent will induce some change in enzyme specificity. Moreover, secondary residues of enzyme-binding sites may also exert a significant influence on specificity since, as obsd. in this study, chymotrypsin exhibited high affinity for cationic substrates and cationic **inhibitors** as well in apolar solvents.
ST chymotrypsin kinetics specificity org solvent; **serine protease** kinetics specificity org solvent

L10 ANSWER 22 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1988:220161 CAPLUS
DN 108:220161
TI The effect of serine esterase inhibitors on ionophore-induced histamine release from human pulmonary mast cells
AU Hultsch, T.; Ennis, M.; Heidtmann, H. H.
CS Inst. Theor. Surg., Univ. Marburg, Marburg, D-3550, Fed. Rep. Ger.
SO Agents and Actions (1988), 24(3-4), 198-200
CODEN: AGACBH; ISSN: 0065-4299
DT Journal
LA English
AB The serine **proteases** tryptase and chymase are present in human pulmonary mast cells. About 10-100-fold more tryptase than chymase is found in these cells. A dose-dependent **inhibition** of A23187-induced histamine release from dispersed human lung mast cells was obsd. after pretreatment with the **serine protease inhibitor** diisopropylfluorophosphate (DFP) or the chymotrypsin-like enzyme **inhibitor** N-tosyl-L-**phenylalanine** chloromethylketone (TPCK) but not with the trypsin-like enzyme **inhibitor** N-tosyl-L-**lysine** chloromethylketone (TLCK). Thus, a chymase is probably an important factor in the late phase of human lung mast cell activation.

L10 ANSWER 23 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1987:418274 CAPLUS
DN 107:18274
TI .beta.-Adrenergic receptor modification with **serine**

protease inhibitors
AU Voeikov, V. L.; Udovichenko, I. P.; Kiselev, O. G.; Prokhorova, I. A.
CS Biol. Fac., M. V. Lomonosov Moscow State Univ., Moscow, USSR
SO Biologicheskie Membrany (1987), 4(4), 438-42
CODEN: BIMEE9; ISSN: 0233-4755
DT Journal
LA Russian
TI .beta.-Adrenergic receptor modification with **serine protease inhibitors**
AB The proteinase inhibitors diisopropylfluorophosphate (DFP), phenylmethanesulfonylfluoride) (PMSF), N-.alpha.-p-tosyl-L-**lysine** chloromethyl ketone (TLCK), or N-p-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK) decreased dihydroalprenolol binding by highly purified bovine cerebellum .beta.-adrenergic receptors reconstituted into phospholipid vesicles. TLCK, PMSF, and DFP, but not TPCK, also decreased ligand binding by .beta.-receptors from bovine cerebellum membrane and TLCK and TPCK decreased that by frog erythrocyte membrane, but none of the proteinase inhibitors affected ligand binding by intact frog erythrocytes. [3H]DFP covalently labeled reconstituted .beta.-receptors. TLCK, isoproterenol, and, to a lesser extent, propranolol abolished this labeling. A comparison of the primary structure of the mammalian .beta.-receptor and chymotrypsin revealed 3 short regions of homol., 2 of which are adjacent to His and Asp residues of the active center of chymotrypsin and 1 includes the active Ser195 which coincides with Ser408 of the receptor. Apparently, .beta.-adrenergic receptors possess a site similar to the active site of serine proteinases. This site is likely to be localized on the cytoplasmic surface of the cell membrane.
IT Receptors
RL: PROC (Process)
(.beta.-adrenergic, **serine protease inhibitors** modification of)
IT 7683-59-2
RL: BIOL (Biological study)
(.beta.-adrenergic receptor binding of **protease inhibitor** abolition by)

L10 ANSWER 24 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1983:486507 CAPLUS
DN 99:86507
TI Analysis of proteases involved in phagocytic activity of macrophages through the use of various amino acid esters
AU Nihira, Shinichi; Koyama, Jiro
CS Fac. Pharm. Sci., Hokkaido Univ., Sapporo, 060, Japan
SO Journal of Biochemistry (Tokyo, Japan) (1983), 94(2), 565-73
CODEN: JOBIAO; ISSN: 0021-924X
DT Journal
LA English
AB The **inhibitory** effects of various amino acid esters on the phagocytic activity of guinea pig peritoneal macrophages were studied with antibody-coated 51Cr-labeled sheep erythrocytes (51Cr-EAb) as well as 125I-labeled-.alpha.-amylase complexed with homologous IgG2 antibody (Ag-Ab complex). The intracellular uptake of 51Cr-EAb was markedly **inhibited** by the chymotrypsin substrates, N-acetyl-L-**phenylalanine** Et ester (Ac-Phe-OEt), N-acetyl-L-tryptophan Et ester (Ac-Trp-OEt), and N-benzoyl-L-tyrosine Et ester (Bz-Tyr-OEt), but not by N-acetyl-L-tyrosine Et ester (Ac-Tyr-OEt) and not by the trypsin substrates, N-.alpha.-acetyl-L-arginine Me ester, N-.alpha.-benzoyl-L-arginine Et ester (Bz-Arg-OEt), or N-.alpha.-acetyl-L-**lysine** Me ester. When phagocytosis of the Ag-Ab complex was assayed by measuring the amt. of digested products released from macrophage cells, Ac-Tyr-OEt also **inhibited** it as markedly as Ac-Phe-OEt, Ac-Trp-OEt, and Bz-Tyr-OEt did, whereas Bz-Arg-OEt again did not show any effect. The results of anal. of the intracellular fate of the Ag-Ab complex taken up

by macrophages, through the use of anal. d. gradient fractionation of the homogenized cells, suggest that Ac-Phe-OEt **inhibits** the ingestive process since the distribution of Ag-Ab complex showed a single peak, closely accompanying the plasma membrane. Ac-Tyr-OEt, on the other hand, caused a marked accumulation of Ag-Ab complex in the lysosome fraction, reflecting the **inhibition** of intralysosomal digestion of the complex. These results may classify the chymotrypsin substrates tested into 3 groups: 1) Ac-Phe-OEt and Ac-Trp-OEt **inhibiting** the ingestive process in phagocytosis, probably more strongly than the digestive process; 2) Bz-Tyr-OEt **inhibiting** both the ingestive and digestive processes and 3), Ac-Tyr-OEt **inhibiting** the digestive process alone. In addn., this classification of the chymotrypsin substrates may support the hypothesis that a certain chymotrypsin-like **serine protease** with a high substrate-specificity is involved in the ingestive process of immune complexes in macrophages.

IT 840-97-1 971-21-1 2361-96-8 2382-80-1 3483-82-7 6072-02-2 6072-07-7
RL: BIOL (Biological study)
(macrophage phagocytosis **inhibition** by, chymotrypsin-like **protease** in)

L10 ANSWER 25 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1983:87001 CAPLUS
DN 98:87001
TI Effect of an extract of Nereis virens on mammalian spermatozoa
AU Gordon, Mildred; Morris, Eugene G.; Stark, Freddy; Williams, William L.; Young, Ron J.
CS Sch. Biomed. Educ., City Coll., New York, NY, 10031, USA
SO Gamete Research (1982), 6(4), 353-63
CODEN: GAMRDC; ISSN: 0148-7280
DT Journal
LA English
AB Epididymal sperm of the mouse, rat, and guinea pig and ejaculated sperm of rabbits are cleaved at the head-tail junction by an ext. of N. virens. Electron microscopy shows that the ext. acts on the filaments connecting the capitulum of the tail with the basal plate lining the nuclear envelope. Following detachment, the basal plate remains with the head. The ext. contains **proteases** as indicated by hydrolysis of tosyl arginine Me ester (TAME), BAEE, and Azocoll, a general **protease** substrate. The hydrolysis of TAME is **inhibited** by TLCK, a trypsin **inhibitor**, but TLCK does not prevent head-tail sepn. by the Nereis ext. Similarly, tosyl **phenylalanine** chloromethyl ketone (TPCK), a chymotrypsin **inhibitor**, and phosphoramidon and leucyltryptophan, both thermolysin and acrolysin **inhibitors**, either singly or in combination, do not prevent hydrolysis of Azocoll. Head-tail sepn. activity of the ext. was **inhibited** by dithiothreitol, which reduces disulfide bonds, and phenylmethyl sulfonyl fluoride, an **inhibitor** of serine **proteases**. Evidently, the ext. is a mixt. of **proteases**, one being a **serine protease** similar to trypsin. Digestion of the connecting filaments with pure **proteases**, trypsin and Staphylococcus aureus V8 **protease**, has yielded the following information on the proteins of the filaments. The accessibility of arginine and (or) **lysine** peptide bonds to enzyme action is highest in rat sperm filaments, whereas those in the filaments of mouse, rabbit, and guinea pig sperm are less accessible than those in the rat. Another possibility is that the total content of arginine and (or) **lysine** varies among the species. The most dramatic difference is the enzymic action on glutamyl peptide bonds of the filaments, the order being: mouse > rat > rabbit, with guinea pig sperm filaments completely resistant over the time course of the expt.

L10 ANSWER 26 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1980:38507 CAPLUS
DN 92:38507
TI **Serine protease inhibitors inhibit** superoxide production by human polymorphonuclear leukocytes and monocytes stimulated by various surface active agents
AU Kitagawa, Seiichi; Takaku, Fumimaro; Sakamoto, Shinobu
CS Dep. Hematol., Jichi Med. Sch., Minamikawachi, 329-04, Japan
SO FEBS Letters (1979), 107(2), 331-4
CODEN: FEBLAL; ISSN: 0014-5793
DT Journal
LA English
TI **Serine protease inhibitors inhibit** superoxide production by human polymorphonuclear leukocytes and monocytes stimulated by various surface active agents
AB Serine proteinases (I) of polymorphonuclear leukocyte (PMN) and monocyte cell membranes apparently are involved in superoxide release by these cells. I inhibitors (phenylmethylsulfonylfluoride, L-1-tosylamido-2-phenylethyl chloromethyl ketone, and N-.alpha.-.pi.-tosyl-L-**lysine** chloromethyl ketone) and synthetic substrates (N-benzoyl-L-tyrosine Et ester and p-tosyl-L-arginine Me ester) inhibited superoxide prodn. by human PMNs and monocytes as induced by the surface active agents wheat germ agglutinin, N-formylmethionyl **phenylalanine**, phorbol myristate acetate, Ca ionophore A23187, and phospholipase C (the latter 2 compds. were active only on PMNs and not on monocytes). The action mechanism of the various superoxide inducers are different and this difference was reflected in the different degrees of inhibition of superoxide release by I inhibitors and substrates.

L10 ANSWER 27 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1979:470659 CAPLUS
DN 91:70659
TI Purification, characterization and localization of **serine protease** of Morris hepatoma 8999
AU Banno, Yoshiko; Morris, Harold P.; Katunuma, Nobuhiko
CS Sch. Med., Tokushima Univ., Tokushima, Japan
SO European Journal of Biochemistry (1979), 97(1), 11-21
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
TI Purification, characterization and localization of **serine protease** of Morris hepatoma 8999
AB A **serine protease** of hepatoma 8999, isolated in the mitochondrial fraction, was purified and crystd. The purified enzyme was apparently homogeneous on ultracentrifugal anal. and polyacrylamide disc gel electrophoresis. The ratio of absorbance at 280 nm and 260 nm, A280/A260, was 1.90 and the absorption coeff., A2801%, was 10.5 cm-1 estd. from dry. wt. measurements. The sedimentation coeff. was 2.23 S and the mol. wt. was 24,000. The enzyme contained twice as much **lysine**, arginine, and histidine as chymotrypsinogen, but had a very similar amino acid compn. to **serine protease** from skeletal muscle. The isoelec. point was pH 10.6. The substrate specificity of the enzyme was the same as that of chymotrypsin A. The Km and kcat values for N-acetyl-L-tyrosine Et ester, N-acetyl-L-**phenylalanine** Et ester, and N-acetyl-L-tryptophan Et ester were 0.35 mM and 10.69 s-1, 0.38 mM and 10.7 s-1, and 0.11 mM and 11.8 s-1, resp. The activity was completely **inhibited** by phenylmethylsulfonyl fluoride and partially **inhibited** by tosylphenylalanine chloromethyl ketone. The enzyme was located in different granules from the intracellular particules (light and heavy mitochondrial fraction) by sucrose d. gradient centrifugation, and it was stained in mast cells of the hepatoma 8999 by the immunofluorescent technique. Serine **proteases** were present in different amts. in various organs of rat. The enzyme from hepatoma 8999

gave a single band that fused completely with those of the enzymes from skeletal muscle, heart, liver, and kidney, resp., on Ouchterlony double-diffusion anal. using antiserum to the cryst. enzyme of hepatoma 8999; the enzyme from small intestine did not react with the antiserum.

ST **serine protease** hepatoma; chymotrypsin protease hepatoma

L10 ANSWER 28 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1978:457216 CAPLUS
DN 89:57216
TI **Inhibition** of bovidae oocyte meiosis by **serine protease inhibitors**
AU Jagiello, Georgiana; Ducayen, Mercedes; Goonan, William; Downey, Susan
CS Cent. Reprod. Sci., Columbia Univ. Coll. Physicians Surg., New York, NY, USA
SO Proceedings of the Society for Experimental Biology and Medicine (1978), 157(4), 550-2
CODEN: PSEBAA; ISSN: 0037-9727
DT Journal
LA English
TI **Inhibition** of bovidae oocyte meiosis by **serine protease inhibitors**
AB In bovine oocytes in vitro, the approx. concns. required to **inhibit** maturation of 50% of the oocytes relative to controls were 0.1 mM for N-p-tosyl-L-**lysine** chloromethyl ketone, a trypsin **inhibitor**, phenylmethylsulfonyl fluoride, an **inhibitor** of esterase involved in the phosphorylation of serine residues, and di-Ph carbamyl chloride, a chymotrypsin **inhibitor**, 0.3 mM for N-p-tosyl-L-**phenylalanine** chloromethyl ketone, a chymotrypsin **inhibitor**; and 3.0 mM for N-tosyl arginine Me ester-HCl, a trypsin substrate analog. The natural **serine protease inhibitor** serum .alpha.u-antitrypsin (10 mg/mL) also prevented maturation in 94 oocytes. Serine **proteases** may be involved in bovine oocyte maturation.
ST **serine protease** egg meiosis; trypsin egg meiosis; chymotrypsin egg meiosis

L10 ANSWER 29 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1974:92547 CAPLUS
DN 80:92547
TI Heterogeneity of Streptomyces griseus **protease**. Isolation and characterization of an alkaline **serine protease** from commercial Pronase-P derived from Streptomyces griseus Kl
AU Bauer, Carl Axel; Lofqvist, Bo
CS Biochem. 1, Chem. Cent., Lund, Swed.
SO Acta Chemica Scandinavica (1947-1973) (1973), 27(9), 3147-66
CODEN: ACSAA4; ISSN: 0001-5393
DT Journal
LA English
TI Heterogeneity of Streptomyces griseus **protease**. Isolation and characterization of an alkaline **serine protease** from commercial Pronase-P derived from Streptomyces griseus Kl
AB A proteolytic enzyme was isolated from Pronase-P by gel filtration on Sephadex G-75 superfine. The yield was almost optimal and the specific activity of the enzyme was const. throughout the isolation procedure and storage. Anal. polyacrylamide gel electrophoresis at pH 6.8 and 8.5 failed to reveal any impurities in the prepn. When the enzyme was concd. 5-10 fold, 2 minor contaminants were detected. They were estd. by staining to constitute < 2% and by enzymic activity < 1%. The binding of Ca2+ to the enzyme was found to be nonstoichiometric, and leading to a higher electrophoretic mobility with increasing Ca2+-content in the buffer. In Ca2+-free media the enzyme has an isoelec. point just > 7. The mol. wt. was estd. at 18,000. The most striking feature of the amino

acid anal. was that no **lysine** was detected. The enzyme was most stable in Ca2+-contg. buffers of neutral pH. In such buffers, the enzyme was also stable in the pH range 5-11, in this respect being similar to elastase. The pH optimum of the enzyme towards glutarylphenylalanine p-nitroanilide was between pH 10 and 11. The enzyme was **inhibited** completely by diisopropyl fluorophosphate, and partly by **inhibitors** normally considered to be site-specific for either chymotrypsin or elastase. The enzyme was highly active towards acetyl-L-tyrosine Et ester, (carbobenzoxy)tyrosine p-nitrophenyl ester, and glutaryl-L-**phenylalanine** p-nitroanilide. It was also active towards acetyl-alanyl-alanyl-alanine Me ester and Congo Red elastin as well as towards many other substrates. The activity towards casein at pH 7.5 and pH 10 was approx. identical. Amidase activity of the enzyme was low. The enzyme was classified as an alk. **serine protease** with broad substrate specificity, showing similarities with both chymotrypsin and elastase. The results are discussed in relation to earlier investigations on this and similar enzymes.

ST alk protease Streptomyces; Pronase **serine protease** component

=> d bib hit 1-15

L10 ANSWER 1 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 2001:839395 CAPLUS
DN 136:116732
TI Involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture
AU Mitsui, Chizu; Sakai, Kazuhisa; Ninomiya, Takafumi; Koike, Tatsuro
CS Molecular Neurobiology Laboratory, Graduate School of Science, Hokkaido University, Sapporo, 060-0810, Japan
SO Journal of Neuroscience Research (2001), 66(4), 601-611
CODEN: JNREDK; ISSN: 0360-4012
PB Wiley-Liss, Inc.
DT Journal
LA English
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture

AB Superior cervical ganglion (SCG) cells from neonatal rats underwent apoptosis upon treatment with colchicine, a microtubule-disrupting agent. Western blotting and activity measurements showed that caspase-3 was indeed activated, but its peptide **inhibitor** (Ac-DEVD-CHO) neither suppressed nuclear fragmentation nor rescued the neurons from cell death. Z-VAD-fmk, the general **inhibitor** of caspases, prevented nuclear fragmentation and delayed the cell death. Moreover, N-.alpha.-tosyl-L-**lysine** chloromethyl ketone (TLCK), but not N-.alpha.-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK), prevented nuclear fragmentation and provided neuronal protection as well. The combination of both z-VAD-fmk and TLCK provided a long-term neuronal protection (>4 days); whereas neither one alone could do so, suggesting that there are both caspase-dependent and -independent pathways. TLCK-sensitive **serine protease** is also likely to act upstream of caspase-3 in a caspase-dependent pathway. Electron microscopic observations demonstrated that z-VAD-fmk suppressed nuclear fragmentation and improved mitochondrial swelling, but failed to prevent vesicular formation, which resulted in a slowly-occurring necrosis. More importantly, TLCK effectively blocked this abundant vesicular formation along with suppressing chromatin condensation. Thus, the combination of both conferred a nearly normal morphol., which is consistent with the results of cell survival expts. These findings clearly indicate that TLCK-sensitive **serine protease** plays multiple roles in

caspase-dependent and -independent pathways of colchicine-induced cell death, and suggest a novel mechanism underlying a necrotic pathway involving ER swelling and vesicular formation.

ST **serine protease** sympathetic neuron apoptosis necrosis caspase

IT Nerve, disease
(death; involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)

IT Nervous system
(disease; involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)

IT Apoptosis
Mitochondria
Necrosis
Newborn
(involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)

IT Cell death
(neuron; involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)

IT Ganglion
(superior cervical sympathetic; involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)

IT 37259-58-8, **Serine protease**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TLCK-sensitive; involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)

IT 402-71-1, N-.alpha.-Tosyl-L-phenylalanine chloromethyl ketone 2364-87-6
169592-56-7, Caspase-3 220644-02-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)

IT 64-86-8, Colchicine
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)

L10 ANSWER 2 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 2000:478833 CAPLUS
DN 134:14577
TI Identification and characterisation of the excreted/secreted serine proteases of larvae of the Old World screwworm fly, Chrysomya bezziana
AU Muharsini, Sri; Sukarsih; Riding, George; Partoutomo, Sutijono; Hamilton, Susan; Willadsen, Peter; Wijffels, Gene
CS CSIRO Tropical Agriculture, Molecular Animal Genetics Centre, Level 3, Gehrmann Laboratories, University of Queensland, Queensland, 4072, Australia
SO International Journal for Parasitology (2000), 30(6), 705-714
CODEN: IJPYBT; ISSN: 0020-7519
PB Elsevier Science Ltd.
DT Journal
LA English
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Serine **proteases** are the major proteolytic activity excreted or secreted from Chrysomya bezziana larvae as demonstrated by gelatin gel analyses and the use of specific substrates, benzoyl-Arg-p-nitroanilide and succinyl-Ala-Ala-Pro-Phe-p-nitroanilide. Serine **proteases**

were identified through their **inhibition** by 4-(2-aminoethyl)-benzene sulfonyl fluoride and classified as trypsin- and chymotrypsin-like on the basis of **inhibition** by tosyl-L-**lysine** chloromethyl ketone and tosyl-L-**phenylalanine** chloromethyl ketone, resp. Like most insect serine **proteases**, the C. bezziana enzymes were active over broad pH range from mildly acidic to alk. The excreted or secreted serine **proteases** were purified by affinity chromatog. using soybean trypsin **inhibitor**. A different subset of the serine **proteases** was isolated by salt elution from washed larval peritrophic matrixes. Aminoterminal sequencing identified both trypsin and chymotrypsin-like sequences in the excreted or secreted pool with the latter being the dominant **protease**, whereas trypsin was the dominant species in the peritrophic matrix eluant. These results suggest that trypsin was possibly preferably adsorbed by the peritrophic matrix and may act as a final proteolytic processing stage as partially digested and ingested polypeptides pass through the peritrophic matrix. Immunoblot anal. on dissected gut tissues indicated that the anterior and posterior midguts were the main source of the serine **proteases**, although a novel species of 32 kDa was predominantly assocd. with the peritrophic matrix. **Proteases** are a target for a partially protective immune response and understanding the complexity of the secreted and digestive **proteases** is a necessary part of understanding the mechanism of the host's immunol. defense against the parasite.

ST screwworm fly **serine protease** chymotrypsin trypsin

IT 37259-58-8P, **Serine protease**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(trypsin- and chymotrypsin-like; identification and characterization of excreted/secreted **serine** proteases of larvae of Old World screwworm fly, Chrysomya bezziana)

L10 ANSWER 3 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 2000:201999 CAPLUS
DN 132:306250
TI A role for serine proteases in mediating phorbol ester-induced differentiation of HL-60 cells
AU Bestilny, Leslie J.; Riabowol, Karl T.
CS Departments of Biochemistry & Molecular Biology and Oncology, The University of Calgary Health Sciences Centre, Calgary, AB, T2N 4N1, Can.
SO Experimental Cell Research (2000), 256(1), 264-271
CODEN: ECREAL; ISSN: 0014-4827
PB Academic Press
DT Journal
LA English
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Treatment of human HL-60 promyelocytic leukemia cells with the phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA), results in increases in proteolytic activity and maturation toward the monocytic lineage. To investigate the potential roles that different classes of **proteases** play in the monocytic differentiation of HL-60 cells, cells were treated with TPA in the presence of various **serine** and cysteine **protease inhibitors**. The **serine protease inhibitors**, 4-(2-aminoethyl)-benzenesulfonyl fluoride (AEBSF), N-.alpha.-tosyl-**phenylalanine** chloromethyl ketone (TPCK), and N-.alpha.-tosyl-**lysine** chloromethyl ketone (TLCK), repressed a no. of phenotypic markers of monocytic differentiation including surface expression of CD11b integrin, cell aggregate formation, cell cycle exit, and cell death. CD11b was not detected at the cell surface by FACS anal. up to 24 h after induction of differentiation; however, both CD11b mRNA and protein were present. Down-regulation of

AN 1999:126886 CAPLUS
DN 130:196584
TI Preparation of aniline derivatives as calcium channel blockers
IN Hu, Lain-Yen; Rafferty, Michael Francis; Ryder, Todd Robert
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 137 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9907689	A1	19990218	WO 1998-US15907	19980729	<--
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	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
	AU 9887627	A1	19990301	AU 1998-87627	19980729	<--
	ZA 9807144	A	19990510	ZA 1998-7144	19980807	<--
	US 6251918	B1	20010626	US 1999-402196	19990929	
	US 2001023249	A1	20010920	US 2001-769798	20010125	
	US 6495715	B2	20021217			
	US 2003060632	A1	20030327	US 2002-252854	20020923	
PRAI	US 1997-55251P	P	19970811			
	US 1998-82358P	P	19980420			
	WO 1998-US15907	W	19980729			
	US 1999-402196	A3	19990929			
	US 2001-769798	A3	20010125			

OS MARPAT 130:196584
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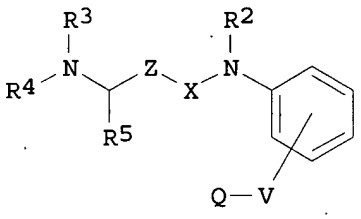

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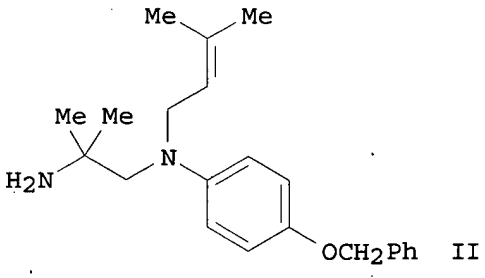

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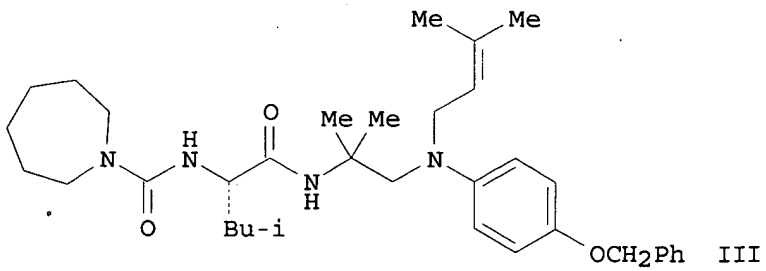


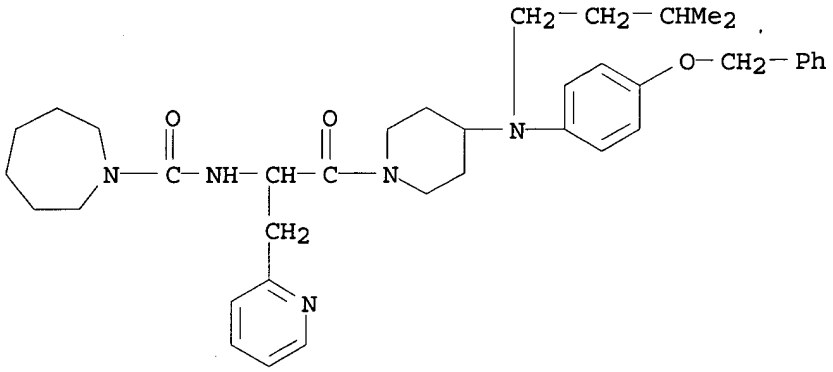
III

AB The invention provides compds. that block calcium channels. In

particular, the invention claims compds. I [Z = CH2 or CO; X = cycloalkylene, (un)substituted heterocycloalkylene, imino or iminoalkylene, certain piperidinediyl or pyrrolidinediyl radicals or their alkylene derivs.; Q = H, (un)substituted aryl, heteroaryl, cycloalkyl, alkyl, heterocycloalkyl; V = O(CH2)n or (CH2)nO, O, (CH2)n, CH:CH, NH(CH2)n or (CH2)nNH or derivs.; R2 = H, alkenyl, cycloalkenyl, (un)substituted Ph, alkyl, cycloalkyl, or Ph; R3 = H, alkyl, alkenyl; R4 = H, cyclo-(CH2)mNCO, alkyl, alkenyl, (un)substituted Ph, heteroaryl, or cycloalkyl; or NR3R4 = 5- to 7-membered ring with an optional addnl. heteroatom; R5 = alkyl, (un)substituted Ph or heteroaryl; m = 1-3; n = 0-3] and their pharmaceutically acceptable salts, esters, amides, and prodrugs. The invention also provides methods of using the compds. to treat stroke, cerebral ischemia, head trauma, or epilepsy, and to pharmaceutical compns. that contain the compds. Over 50 synthetic examples are given, and these plus a large no. of addnl. invention compds. are specifically claimed. For instance, N-BOC-.alpha.-aminoisobutyric acid underwent amidation with 4-benzyloxyaniline, followed by redn. of the amide with diborane, N-alkenylation with 4-bromo-2-methyl-2-butene, and acidic deprotection to remove BOC, to give intermediate II. In a sep. prepn., H-Leu-OCH2Ph was treated with triphosgene and hexamethylenamine, then deprotected, to give Hac-Leu-OH (III; Hac = hexamethylenaminocarbonyl). Coupling of II with III using HBTU and DIPEA in DMF gave title compd. IV. The latter blocked calcium flux through N-type Ca2+ channels in IMR-32 neuronal tumor cells in vitro, with IC50 of 0.26 .mu.M. Selected compds. gave 20-100% protection of mice from tonic seizures in a sound chamber, at doses of 10-30 mg/kg i.v.

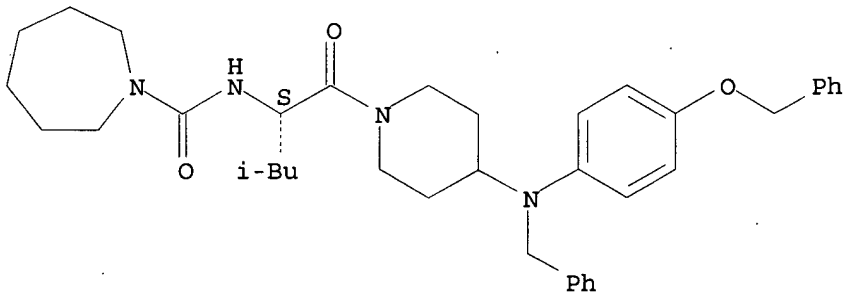
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

RN 220738-25-0 CAPLUS
CN 1H-Azepine-1-carboxamide, hexahydro-N-[2-[4-[(3-methylbutyl)[4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]-2-oxo-1-(2-pyridinylmethyl)ethyl]- (9CI) (CA INDEX NAME)



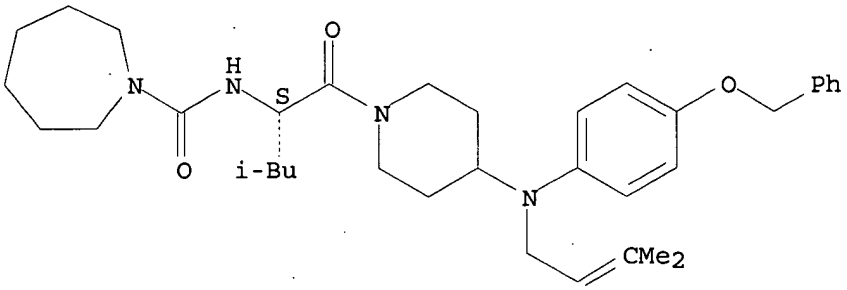
AN 1999:589098 CAPLUS
DN 131:331730
TI Synthesis of a Series of 4-Benzyloxyaniline Analogs as Neuronal N-Type Calcium Channel Blockers with Improved Anticonvulsant and Analgesic Properties
AU Hu, Lain-Yen; Ryder, Todd R.; Rafferty, Michael F.; Feng, M. Rose; Lotarski, Susan M.; Rock, David M.; Sinz, Michael; Stoehr, Sally J.; Taylor, Charles P.; Weber, Mark L.; Bowersox, S. Scott; Miljanich, George P.; Millerman, Elizabeth; Wang, Yong-Xiang; Szoke, Balazs G.
CS Departments of Chemistry Neuroscience Therapeutics and Pharmacokinetics Dynamics and Metabolism, Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company, Ann Arbor, MI, 48105, USA
SO Journal of Medicinal Chemistry (**1999**), 42(20), 4239-4249
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB In this article, the rationale for the design, synthesis, and biol. evaluation of a series of N-type voltage-sensitive calcium channel (VSCC) blockers is described. N-Type VSCC blockers, such as ziconotide, have shown utility in several models of stroke and pain. Modification of the previously reported lead led to several 4-(4-benzyloxylphenyl)piperidine structures with potent in vitro and in vivo activities. In this series, the most interesting compd., (S)-2-amino-1-{4-[(4-benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-4-methyl-pentan-1-one (I), blocked N-type calcium channels (IC50 = 0.67 .mu.M in the IMR32 assay) and was efficacious in the audiogenic DBA/2 seizure mouse model (ED50 = 6 mg/kg, i.v.) as well as the antiwrithing model (ED50 = 6 mg/kg, i.v.). Whole-cell voltage-clamp electrophysiol. expts. demonstrated that compd. I blocked N-type Ca2+ channels and Na+ channels in superior cervical ganglion neurons at similar concns. Compd. I, which showed superior in vivo efficacy, stands out as an interesting lead for further development of neurotherapeutic agents in this series.
IT **220737-68-8P 247130-18-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of 4-benzyloxyaniline analogs as neuronal N-type calcium channel blockers with improved anticonvulsant and analgesic properties)
RN 220737-68-8 CAPLUS
CN 1H-Azepine-1-carboxamide, hexahydro-N-[(1S)-3-methyl-1-[[4-[[4-(phenylmethoxy)phenyl](phenylmethyl)amino]-1-piperidinyl]carbonyl]butyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



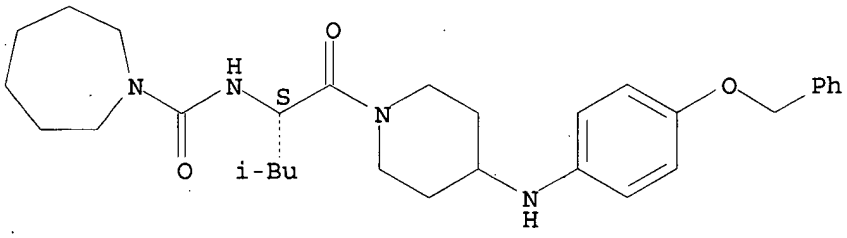
RN 247130-18-3 CAPLUS
CN 1H-Azepine-1-carboxamide, hexahydro-N-[(1S)-3-methyl-1-[[4-[(3-methyl-2-butenyl)[4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]carbonyl]butyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



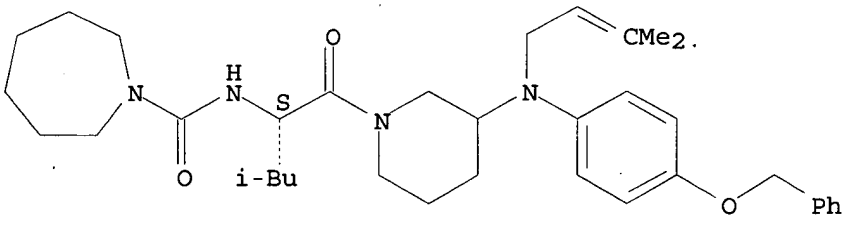
IT **220737-64-4P 250236-95-4P 250236-97-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of 4-benzyloxyaniline analogs as neuronal N-type calcium channel blockers with improved anticonvulsant and analgesic properties)
RN 220737-64-4 CAPLUS
CN 1H-Azepine-1-carboxamide, hexahydro-N-[(1S)-3-methyl-1-[[4-[[4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]carbonyl]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



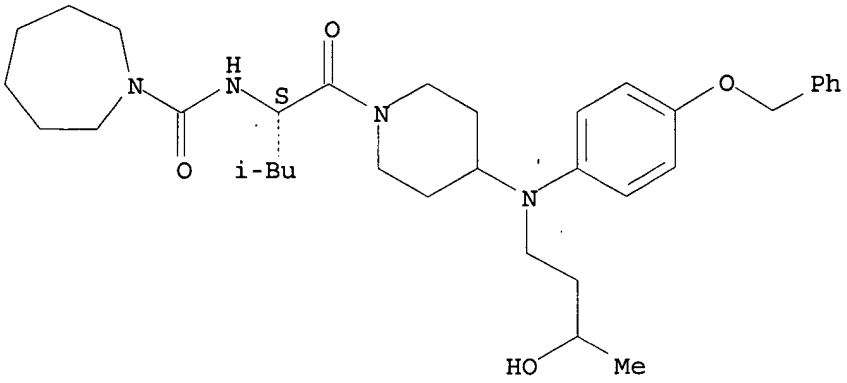
RN 250236-95-4 CAPLUS
CN 1H-Azepine-1-carboxamide, hexahydro-N-[(1S)-3-methyl-1-[[3-[(3-methyl-2-butenyl)[4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]carbonyl]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



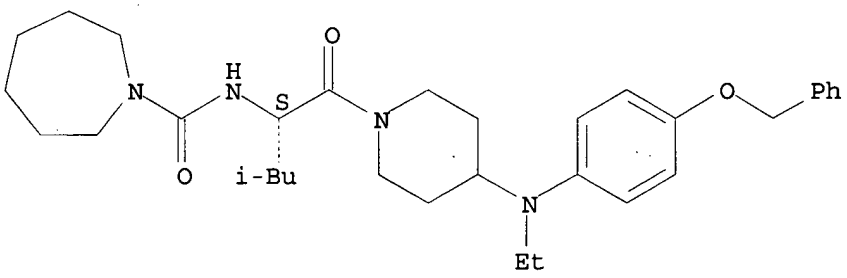
RN 250236-97-6 CAPLUS
CN 1H-Azepine-1-carboxamide, hexahydro-N-[(1S)-1-[[4-[(3-hydroxybutyl)[4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **220737-67-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of 4-benzyloxyaniline analogs as neuronal N-type calcium channel blockers with improved anticonvulsant and analgesic properties)
RN 220737-67-7 CAPLUS
CN 1H-Azepine-1-carboxamide, N-[(1S)-1-[[4-[ethyl[4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]carbonyl]-3-methylbutyl]hexahydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

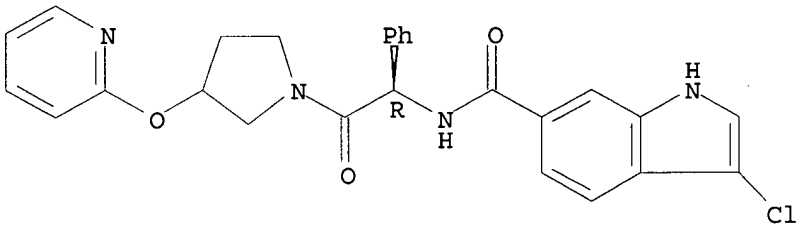
(95-92-1/RN)
L2 240 (100-07-2/BI OR 100-09-4/BI OR 1073-29-6/BI OR 108-95-2/BI OR 109-00-2/BI OR 109-04-6/BI OR 109384-19-2/BI OR 112162-11-5/BI OR 127806-46-6/BI OR 135-02-4/BI OR 138891-54-0/BI OR 141-97-9/BI OR 141518-55-0/BI OR 142121-93-5/BI OR 142121-94-6/BI OR 143-33-9/BI OR 14675-99-1/BI OR 150-19-6/BI OR 150-76-5/BI OR 151-50-8/BI OR 16567-18-3/BI OR 1670-82-2/BI OR 17609-52-8/BI OR 179417-69-7/BI OR 181258-50-4/BI OR 18368-63-3/BI OR 19235-89-3/BI OR 19524-06-2/BI OR 201286-69-3/BI OR 202859-20-9/BI OR 2039-86-3/BI OR 20781-20-8/BI OR 209680-89-7/BI OR 219508-17-5/BI OR 234772-37-3/BI OR 24964-64-5/BI OR 2739-98-2/BI OR 27489-33-4/BI OR 288-47-1/BI OR 298-12-4/BI OR 301225-52-5/BI OR 308386-35-8/BI OR 308386-36-9/BI OR 313487-89-7/BI OR 313487-90-0/BI OR 313487-91-1/BI OR 313487-92-2/BI OR 313487-93-3/BI OR 313487-94-4/BI OR 313487-96-6/BI OR 313487-97-7/BI OR 313487-98-8/BI OR 313487-99-9/BI OR 313488-00-5/BI OR 313488-01-6/BI OR 313488-02-7/BI OR 313488-03-8/BI OR 313488-04-9/BI OR

=> s l2 and indol?
525003 INDOL?
L3 39 L2 AND INDOL?

=> d scan

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(2-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)**
MF C26 H23 Cl N4 O3

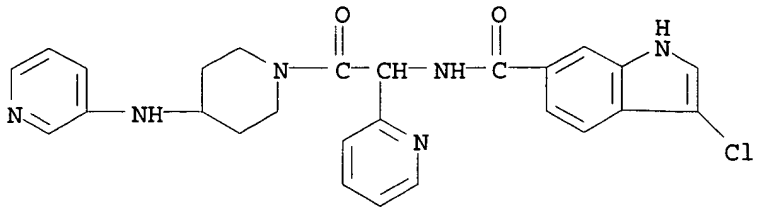
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

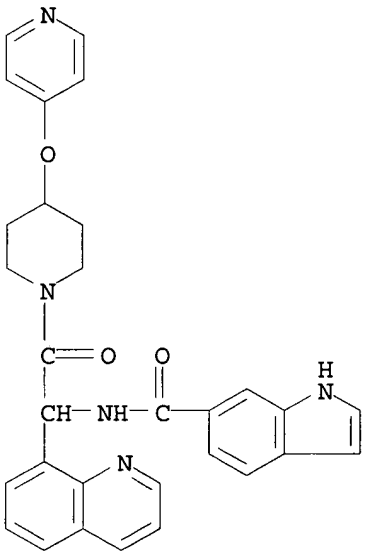
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-chloro-N-[2-oxo-1-(2-pyridinyl)-2-[4-(3-pyridinylamino)-1-piperidinyl]ethyl]-, dihydrochloride (9CI)**
MF C26 H25 Cl N6 O2 . 2 Cl H



● 2 HCl

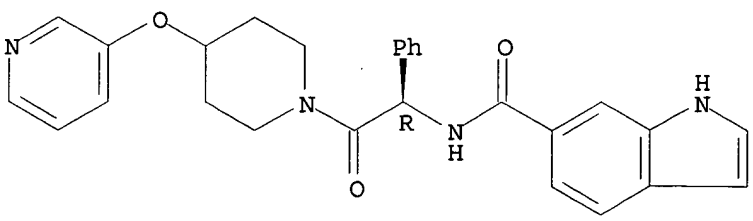
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[2-oxo-2-[4-(4-pyridinyloxy)-1-piperidinyl]-1-(8-quinolinyl)ethyl]-, monohydrochloride (9CI)**
MF C30 H27 N5 O3 . Cl H



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(3-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H26 N4 O3

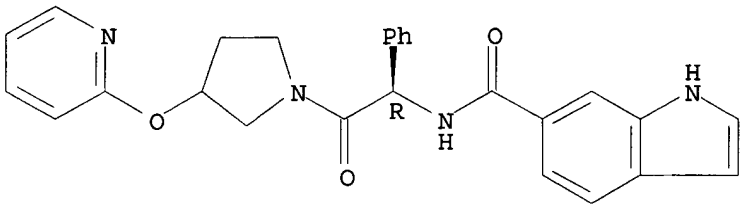
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(2-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)**
MF C26 H24 N4 O3

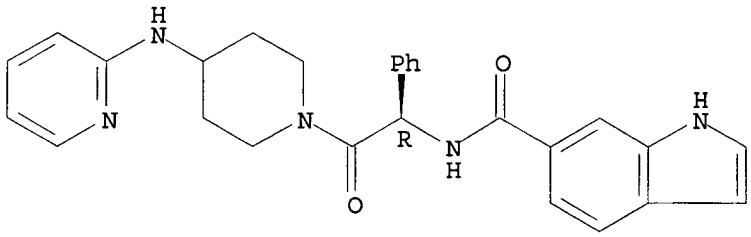
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(2-pyridinylamino)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H27 N5 O2
CI COM

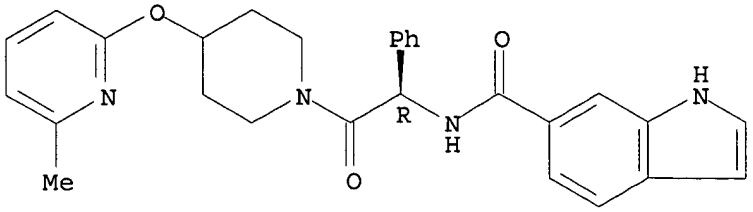
Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-[4-[(6-methyl-2-pyridinyl)oxy]-1-piperidinyl]-2-oxo-1-phenylethyl]-, monohydrochloride (9CI)**
MF C28 H28 N4 O3 . Cl H

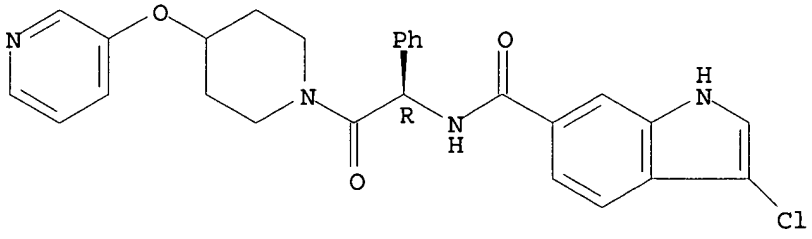
Absolute stereochemistry.



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[4-(3-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H25 Cl N4 O3

Absolute stereochemistry.

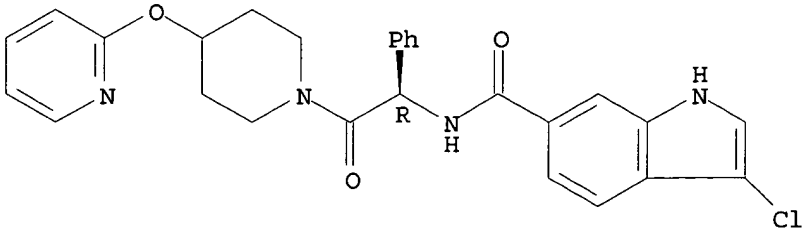


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

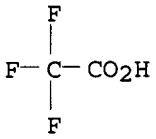
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[4-(2-pyridinyloxy)-1-piperidinyl]ethyl]-, mono(trifluoroacetate) (9CI)**
MF C27 H25 Cl N4 O3 . C2 H F3 O2

CM 1

Absolute stereochemistry.

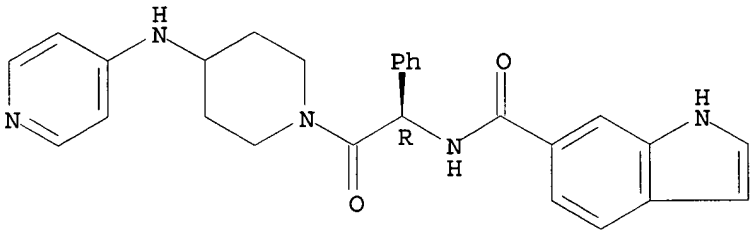


CM 2



L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinylamino)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H27 N5 O2
CI COM

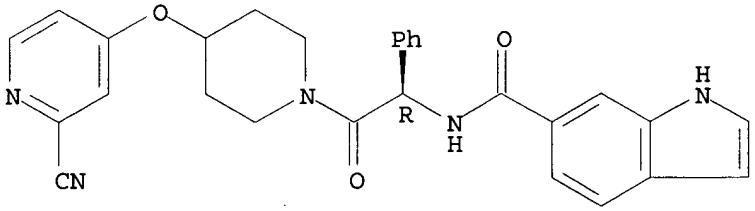
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-[4-[(2-cyano-4-pyridinyl)oxy]-1-piperidinyl]-2-oxo-1-phenylethyl]-, monohydrochloride (9CI)**
MF C28 H25 N5 O3 . Cl H

Absolute stereochemistry.

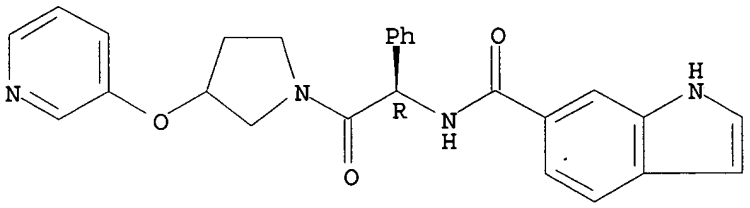


● HCl

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)**
MF C26 H24 N4 O3

Absolute stereochemistry.

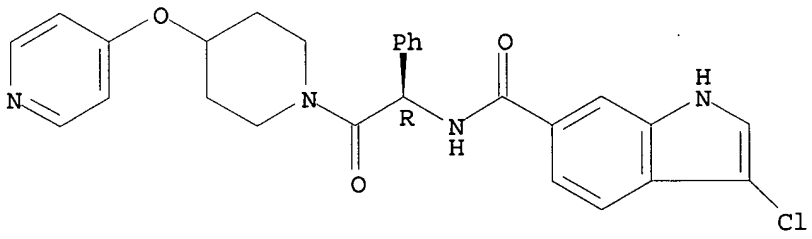


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

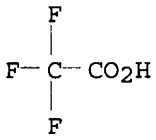
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]-, mono(trifluoroacetate) (9CI)**
MF C27 H25 Cl N4 O3 . C2 H F3 O2

CM 1

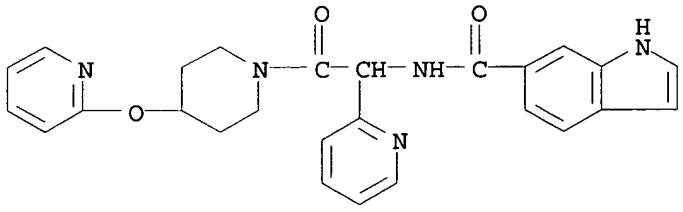
Absolute stereochemistry.



CM 2



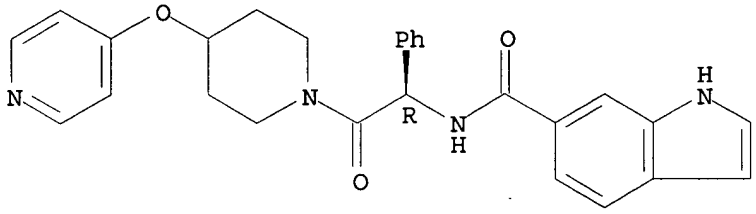
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[2-oxo-1-(2-pyridinyl)-2-[4-(2-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C26 H25 N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]-, monohydrochloride (9CI)**
MF C27 H26 N4 O3 . Cl H

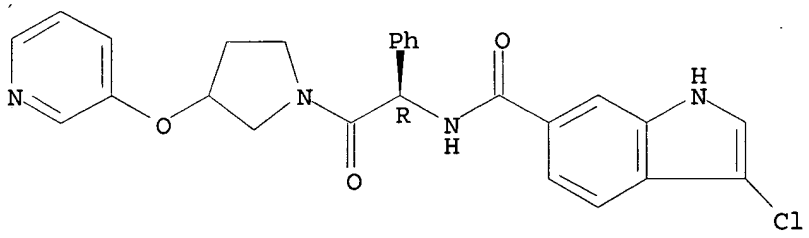
Absolute stereochemistry.



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)**
MF C26 H23 Cl N4 O3

Absolute stereochemistry.

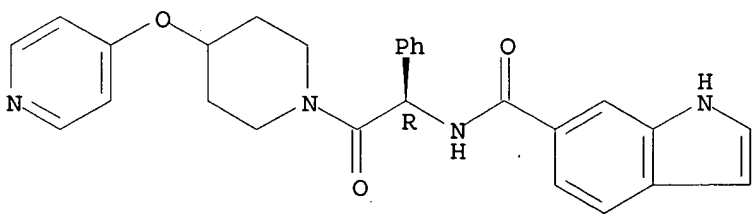


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

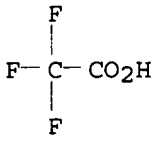
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]-, mono(trifluoroacetate) (9CI)**
MF C27 H26 N4 O3 . C2 H F3 O2

CM 1

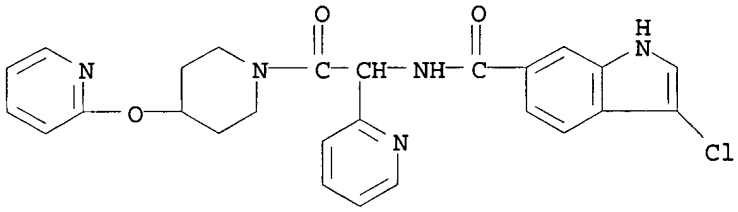
Absolute stereochemistry.



CM 2



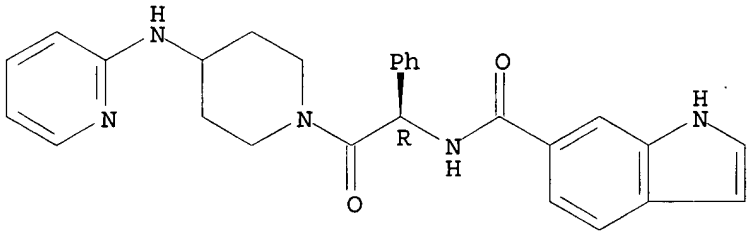
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-chloro-N-[2-oxo-1-(2-pyridinyl)-2-[4-(2-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C26 H24 Cl N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(2-pyridinylamino)-1-piperidinyl]ethyl]-, monohydrochloride (9CI)**
MF C27 H27 N5 O2 . Cl H

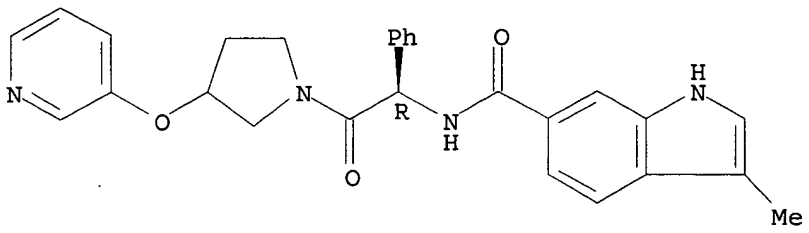
Absolute stereochemistry. Rotation (-).



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-methyl-N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)**
MF C27 H26 N4 O3

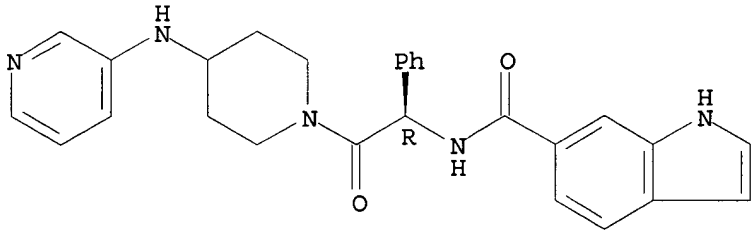
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(3-pyridinylamino)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H27 N5 O2

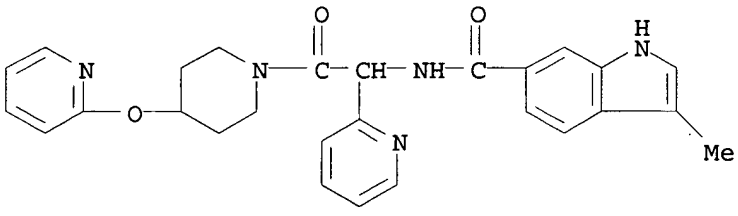
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

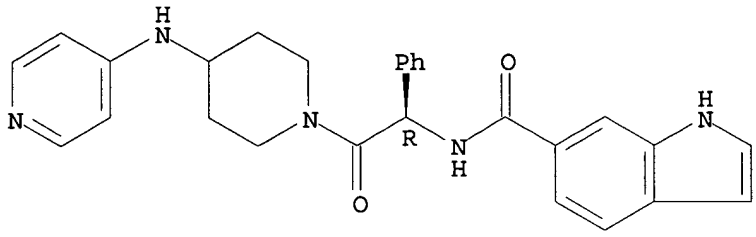
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-methyl-N-[2-oxo-1-(2-pyridinyl)-2-[4-(2-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H27 N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinylamino)-1-piperidinyl]ethyl]-, monohydrochloride (9CI)**
MF C27 H27 N5 O2 . Cl H

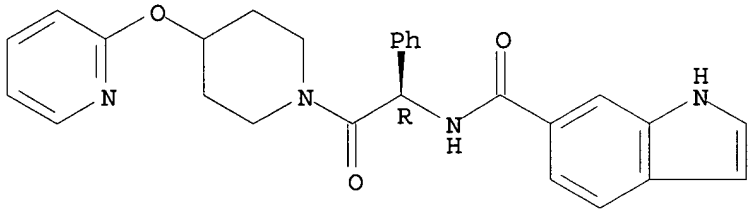
Absolute stereochemistry.



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(2-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H26 N4 O3

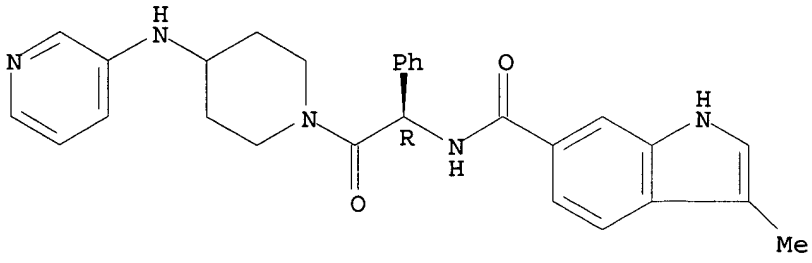
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

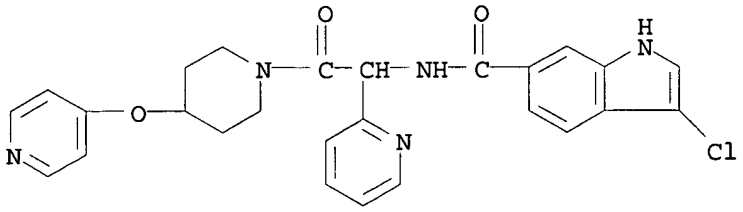
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-methyl-N-[(1R)-2-oxo-1-phenyl-2-[4-(3-pyridinylamino)-1-piperidinyl]ethyl]- (9CI)**
MF C28 H29 N5 O2

Absolute stereochemistry.



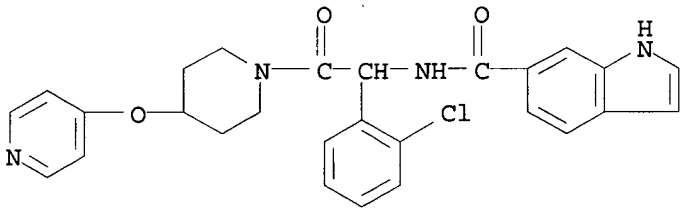
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-chloro-N-[2-oxo-1-(2-pyridinyl)-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C26 H24 Cl N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

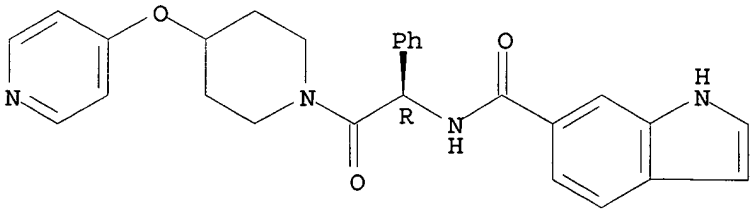
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[1-(2-chlorophenyl)-2-oxo-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H25 Cl N4 O3
CI COM



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H26 N4 O3
CI COM

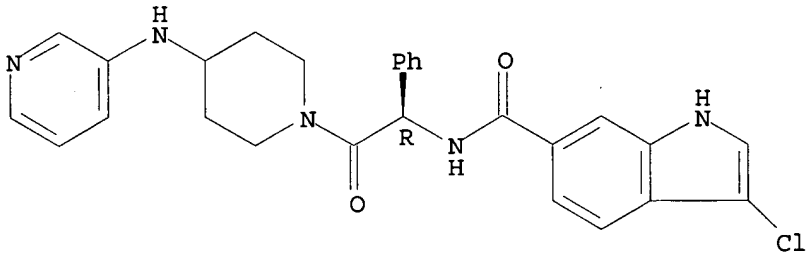
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

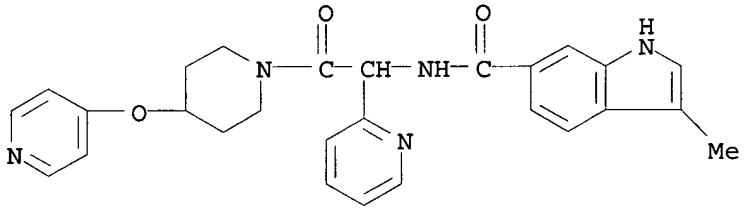
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[4-(3-pyridinylamino)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H26 Cl N5 O2

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-methyl-N-[2-oxo-1-(2-pyridinyl)-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H27 N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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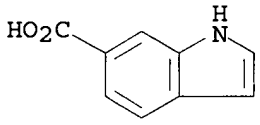


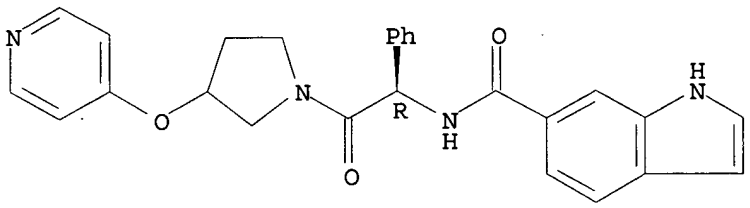
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)**

MF C26 H24 N4 O3

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[2-oxo-1-(2-pyridinyl)-2-[4-(3-pyridinylamino)-1-piperidinyl]ethyl]-, dihydrochloride (9CI)**
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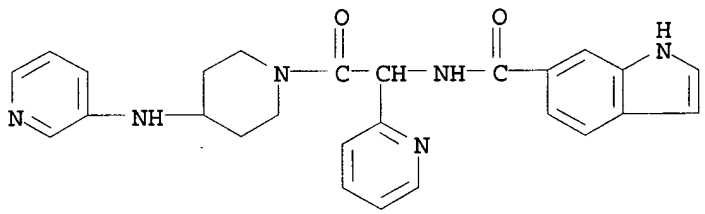
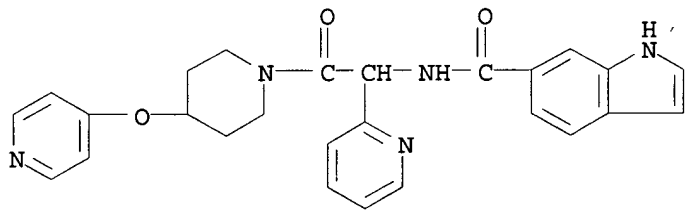


●2 HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[2-oxo-1-(2-pyridinyl)-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)**
MF C26 H25 N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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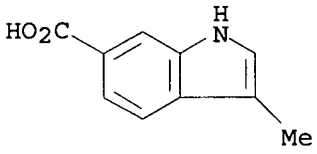
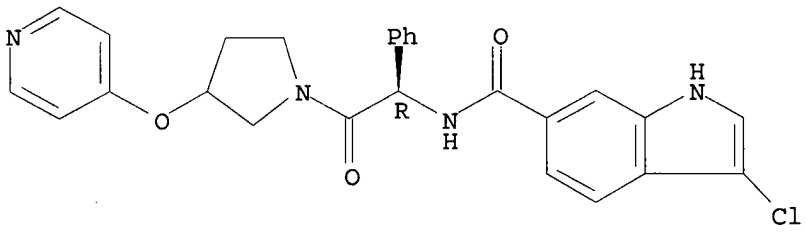


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

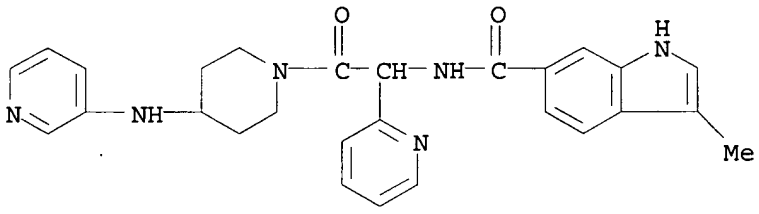
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)**
MF C26 H23 Cl N4 O3

Absolute stereochemistry.



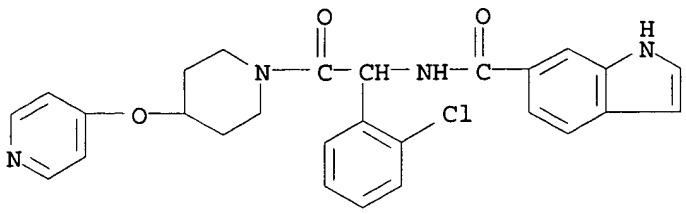
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, 3-methyl-N-[2-oxo-1-(2-pyridinyl)-2-[4-(3-pyridinylamino)-1-piperidinyl]ethyl]- (9CI)**
MF C27 H28 N6 O2



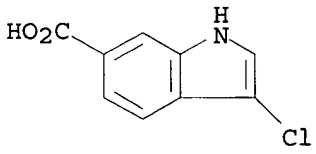
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxamide, N-[1-(2-chlorophenyl)-2-oxo-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]-, monohydrochloride (9CI)**
MF C27 H25 Cl N4 O3 . Cl H



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN **1H-Indole-6-carboxylic acid, 3-chloro- (9CI)**
MF C9 H6 Cl N O2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

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                (WO2001096296/PN)

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L2   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2003 ACS
AN   2001:923758  CAPLUS
DN   136:37946
TI   Preparation of amino acid derivatives as serine protease inhibitors
IN   Liebeschuetz, John Walter; Murray, Christopher William; Young, Stephen
     Clinton; Camp, Nicholas Paul; Jones, Stuart Donald; Wylie, William
     Alexander; Masters, John Joseph; Wiley, Michael Robert; Sheehan, Scott
     Martin; Engel, David Birenbaum; Watson, Brian Morgan
PA   Eli Lilly and Company, USA
SO   PCT Int. Appl., 142 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 13
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PRAI WO 2000-GB2302     W     20000613
     GB 2000-30303      A     20001213
     GB 1999-13823      A     19990614
     US 1999-142064P    P     19990702
     GB 1999-18741      A     19990809
     GB 1999-29553      A     19991214
OS   MARPAT 136:37946
RE.CNT  3     THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2003 ACS
AN   2000:900614  CAPLUS
DN   134:56958
TI   Preparation of amino acid derivatives as serine protease inhibitors
IN   Liebeschuetz, John Walter; Lyons, Amanda Jane; Murray, Christopher
     William; Rimmer, Andrew David; Young, Stephen Clinton; Camp, Nicholas
     Paul; Jones, Stuart Donald; Morgan, Phillip John; Richards, Simon James;
     Wylie, William Alexander; Masters, John Joseph; Wiley, Michael Robert
PA   Eli Lilly and Company, USA; Protherics Molecular Design Limited
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PRAI	GB 1999-13823	A	19990614
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	WO 2001-GB2572	W	20010612
OS	MARPAT 134:56958		

SO PCT Int. Appl., 261 pp.
CODEN: PIXXD2
DT Patent
LA English
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PI	WO 2000076971	A2	20001221	WO 2000-GB2302	20000613	
	WO 2000076971	A3	20010802			
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	US 2002151724	A1	20021017	US 2002-30186	20020204	

AN 1999:184268 CAPLUS
DN 130:223587
TI 1-amino-7-isoquinoline derivatives as serine protease inhibitors
IN Liebeschuetz, John Walter; Wylie, William Alexander; Waszkowycz, Bohdan; Murray, Christopher William; Rimmer, Andrew David; Welsh, Pauline Mary; Jones, Stuart Donald; Roscoe, Jonathan Michael Ernest; Young, Stephen Clinton; Morgan, Phillip John; Camp, Nicholas Paul; Crew, Andrew Philip Austin
PA Proteus Molecular Design Ltd., UK
SO PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 13

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	WO 1998-GB2600	W	19980828			
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OS MARPAT 130:223587
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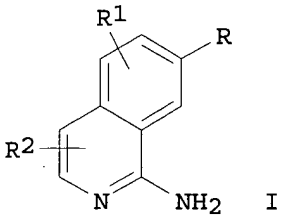


I

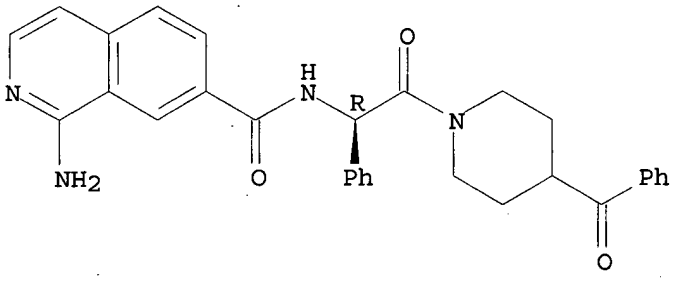
AB Aminoisoquinoline amino acid derivs. I [R1 = H, halo, cyano, nitro, hydroxy, amino, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, thiol, alkylthio, aminosulfonyl, alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or alkylamino (optionally substituted); R2 = H, halo, Me, amino, hydroxy, or oxo; and R is X-X-Y(R7)-L-Lp(D)n, where each X independently is a C, N, O or S atom or a CO, CR1, CR12 or NR1 group; Y is a nitrogen atom or a CR1 group or Y and L taken together form a cyclic group; R7 is a lipophilic group selected from alkyl, alkenyl, mono- or bi-cycloalkyl, aryl, heteroaryl, mono- or bicycloalkylalkyl, mono- or bicycloalkylalkenyl, aralkyl, heteroaryl-alkyl, arylalkenyl, heteroarylalkenyl, all optionally

substituted by a group R1; L is an org. linker group contg. 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic group; Lp is a lipophilic org. group selected from alkyl, heterocyclic, alkenyl, alkaryl, cycloalkyl, polycycloalkyl, cycloalkenyl, aryl, aralkyl or haloalkyl group or a combination of two or more such groups optionally substituted by one or more of oxa, thia, aza or R1 groups; D is a hydrogen bond donor group; and n is 0, 1, or 2] or their 3,4-dihydro derivs. were prepd. as serine protease inhibitors. Thus, 1-aminoisoquinolin-7-oyl-D-phenylglycine-4-methoxybenzylamide was prepd. by amidation of Boc-D-phenylglycine with 4-methylbenzylamine, followed by deprotection and coupling with 1-aminoisoquinoline-7-carboxylic acid trifluoroacetate.

IT **221049-84-9P 221049-99-6P 221050-30-2P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoisoquinoline peptidyl derivs. as serine protease inhibitors)

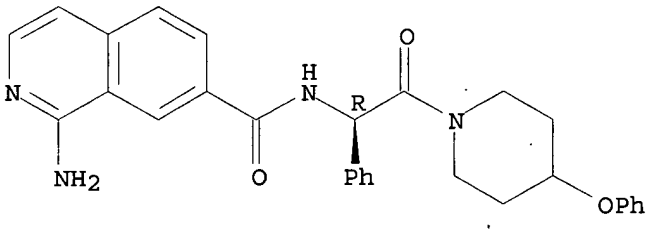
RN 221049-84-9 CAPLUS
CN 7-Isoquinolinecarboxamide, 1-amino-N-[(1R)-2-(4-benzoyl-1-piperidinyl)-2-oxo-1-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



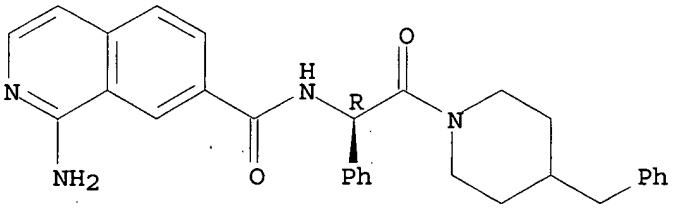
RN 221049-99-6 CAPLUS
CN 7-Isoquinolinecarboxamide, 1-amino-N-[(1R)-2-oxo-2-(4-phenoxy-1-piperidinyl)-1-phenylethyl]- (9CI) (CA INDEX NAME)

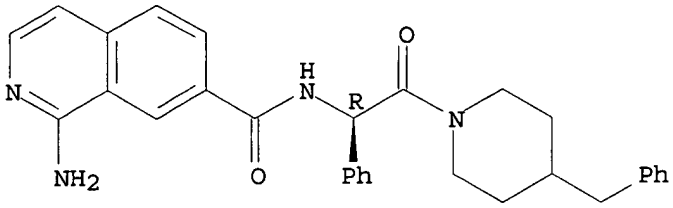
Absolute stereochemistry.



RN 221050-30-2 CAPLUS
CN 7-Isoquinolinecarboxamide, 1-amino-N-[(1R)-2-oxo-1-phenyl-2-[4-(phenylmethyl)-1-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.





RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT